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CIÊNCIAS MÉDICAS

Dinâmicas Familiares, Psicopatologia e Vinculação em Doentes com Polineuropatia Amiloidótica Familiar

Maria Alice Lopes

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

MARIA ALICE SOARES LOPES

DINÂMICAS FAMILIARES, PSICOPATOLOGIA E VINCULAÇÃO EM DOENTES COM POLINEUROPATIA AMILOIDÓTICA FAMILIAR

Tese de Candidatura ao grau de Doutor em Ciências Médicas submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

Orientador – Prof.ª Doutora Paula Freitas

Categoria – professora auxiliar

Afiliação – Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

Coorientador – Prof. Dr. Jorge Sequeiros

Categoria – professor catedrático

Afiliação – Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

Ao Manuel, à Ana, à Salomé e à memória dos meus pais

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NOTA PRÉVIA

Motivações e Justificação

Tenho o privilégio de trabalhar desde 1992 com pessoas com polineuropatia amiloidótica familiar (PAF). Fi-lo fundamentalmente no Hospital de Santo António, na mesma Unidade, que ao longo destes anos foi tendo nomes diferentes: Centro de Estudos de Paramiloidose, Unidade Clínica de Paramiloidose e Unidade Corino de Andrade em anos mais recentes. Pude trabalhar também com estas pessoas no Centro de Genética Preditiva e Preventiva do Instituto de Biologia Molecular e Celular, a convite do Professor Jorge Sequeiros.

O convite feito em 1992 a uma psiquiatra para colaborar na Unidade, então Centro de Estudos de Paramiloidose, onde várias especialidades para além da neurologia integravam já a organização assistencial às pessoas com PAF, demonstra do meu ponto de vista, a sensibilidade que existiu desde muito cedo, para os problemas psicológicos e psiquiátricos destes doentes e das suas famílias. Sensibilidade tanto mais digna de nota quanto era manifesto que a psiquiatria não existia no HSA e a psiquiatria de ligação não era então prática assistencial presente na esmagadora maioria dos hospitais portugueses. Não se usava!

A prática assistencial psiquiátrica e posteriormente também da psicologia, que prossegue desde há mais de 20 anos, veio confirmar a justeza desse convite, ou seja, como eram reais as necessidades de apoio psiquiátrico e psicológico nesta consulta. Desde o início também que esta colaboração foi isso mesmo: uma atividade clínica partilhada com as outras especialidades em que o doente e as famílias são o enfoque comum.

Este trabalho partilhado conduz a uma cultura comum o que significa que a linguagem e a comunicação vão melhorando. Isto é, eu sei o que os meus colegas querem comunicar-me acerca de um paciente (e se não sei, pergunto) e tenho a certeza de que a linguagem, por vezes complicada do âmbito psicológico/psiquiátrico, é também melhor compreendida por eles.

Para esta consulta de psiquiatria, mais tarde também para a de psicologia, agora ambas designadas, e bem, numa abrangente “consulta-PAF/Saúde Mental”, têm sido encaminhados inúmeros doentes, portadores assintomáticos e os seus familiares.

Para além do pendor fortemente assistencial, a Unidade Corino de Andrade tem desde sempre o pendor investigacional. Marcada indubitavelmente pela herança científica e modelar de Corino de Andrade, a investigação por ele iniciada a propósito de uma entidade por ele descrita em primeira mão, tem sido continuada ao longo dos anos com trabalhos científicos que muito têm contribuído para aprofundar o conhecimento da doença.

A tradição investigacional da unidade, o sentimento de me ter sido dado ter uma experiência quase única pelo facto de aqui termos o maior número de doentes e famílias referenciadas, impeliram-me e quase me fizeram sentir obrigada a encetar um estudo mais elaborado dos aspetos psicológicos e relacionais destes doentes e destas famílias.

Muitas dúvidas foram surgindo ao longo da elaboração desta tese. Dúvidas em primeiro lugar sobre a sua pertinência (do ponto de vista pessoal e da minha própria carreira), sobre a escolha dos temas a estudar, ajuste da metodologia aos temas escolhidos e dúvidas sobre a minha capacidade de a realizar e levar a bom (?) porto.

A amplitude de temas a estudar é enorme, porque quase tudo, neste âmbito, está por fazer. A escolha entre sujeitos individuais *vs.* família foi também outra enorme dúvida. Acabamos por fazer uma espécie de compromisso, abrangente e geral.

A história da PAF, história da acumulação e integração sucessiva de conhecimento, história da organização de cuidados cada vez mais sistematizada e complexa, tem no nosso país e nomeadamente no Centro Hospitalar do Porto uma relevante importância. Esta é também uma história de mudanças: do aumento progressivo do conhecimento médico, e do destino e comportamentos das pessoas e famílias afetadas.

É desta história que me sinto fazer parte e para a qual, espero, esta tese possa constituir uma pequena contribuição.

AGRADECIMENTOS

São muitas as pessoas a quem me sinto grata e a quem devo o fato de ter conseguido chegar ao fim desta tarefa. Não conseguirei, seguramente, nomeá-las todas.

Agradeço em primeiro lugar aos meus orientadores, Profª. Doutora Paula Freitas e Prof. Doutor Jorge Sequeiros, o importante suporte e incentivo que me deram ao longo deste processo.

A Dr.ª Teresa Coelho, responsável da Unidade Corino de Andrade, permitiu e forneceu meios e recursos necessários para a elaboração desta tese. A sua gestão dinâmica e o seu interesse pela clínica e investigação da doença são e foram determinantes para a realização de todo o trabalho científico aqui apresentado. Agradeço-lhe, para além de tudo, a sua amizade e confiança.

À Dr.ª Isabel Fonseca devo um incentivo também determinante que me "obrigou" a nunca desistir. Devo-lhe para além disso, o apoio incansável no trabalho estatístico, na elaboração dos resultados e uma paciência ilimitada.

Agradeço à Carla Rodrigues e à Alexandra Sousa a sua colaboração em muitas fases deste trabalho. Estiveram sempre presentes quando precisei, nomeadamente, na resolução das minhas insuficiências com as tecnologias.

Aos que já citei e à Margarida Branco, agradeço a colaboração empenhada, discussão e aperfeiçoamento dos artigos incluídos na tese.

À Vanessa Costa estou grata pela disponibilidade ao apoio nas traduções, sempre que as solicitei.

À Isabel Friães devo a permanente disponibilidade para me ajudar a encontrar as compatibilizações de tempo que fui precisando.

Agradeço a todos as pessoas que foram, generosamente, participantes nos estudos aqui realizados.

À minha família agradeço a paciência ilimitada para as minhas "indisponibilidades", o seu incentivo, o seu carinho e apoio. Sem eles, não teria levado a cabo este desígnio profissional.

RESUMO

A polineuropatia amiloidótica familiar relacionada com a transtirretina (PAF-TTR) ou amiloidose ATTR devida à variante Val30Met, é uma amiloidose sistémica, hereditária, de início tardio. É uma doença rara que embora exista em todo o mundo, tem focos de maior prevalência no noroeste de Portugal na Suécia e no Japão. É uma doença crónica com expressão clínica variável, dominada por uma neuropatia sensitivo-motora e autonómica. Manifesta-se como uma polineuropatia periférica, mas também por sintomas a nível gastrointestinal, olhos, pele, rim, coração, com disfunção sexual precoce e perda de controlo de esfíncteres. Evolui com perda ponderal acentuada, deficiência motora e grande incapacidade física. Se não existir instituição de qualquer tratamento, evolui com perda de autonomia e morte em cerca de 11 anos, em média. Em estádios avançados, os doentes tornam-se completamente dependentes para as atividades de vida diária. Durante muito tempo os doentes tiveram disponíveis apenas tratamentos sintomáticos e paliativos. Atualmente existem alternativas de tratamento, mas não curativas.

As caraterísticas devastadoras da doença, a sua natureza hereditária (autossómica dominante) e o seu início tardio impõem uma sobrecarga psicológica nos doentes e famílias afetadas. Os membros destas famílias vivem, ao longo da sua existência, questões de incerteza quanto ao seu estatuto genético, diagnóstico da doença, escolhas reprodutivas e sorte dos familiares próximos.

Os objetivos desta tese dizem respeito às implicações psicopatológicas que a doença poderá ter sobre os doentes e portadores assintomáticos: estudar acontecimentos de vida decorrentes da doença, avaliar dimensões psicopatológicas, perceber de que modo os acontecimentos de vida influenciam as alterações psicopatológicas, compreender como a vinculação do adulto se estruturava nestas famílias e qual a sua relação com acontecimentos de vida e a psicopatologia; analisar a dinâmica familiar percecionada pelos doentes, portadores e seus cônjuges; comparar as caraterísticas e funcionalidade destas famílias com doentes com esclerose múltipla, doença crónica, neurodegenerativa, não hereditária.

Os participantes foram portadores da “mutação” Val30Met na TTR (109 doentes, 81 assintomáticos e 19 sem diagnóstico ainda estabelecido), seguidos na Unidade Corino de Andrade, do Centro Hospitalar do Porto (CHP); 41 cônjuges; e 34 doentes com esclerose múltipla seguidos em consulta externa de neurologia no CHP.

Para além de Questionário Sociodemográfico, foram avaliados com um Questionário de História da Doença pessoal e Familiar, o *Brief Symptom Inventory-53*, escala de Vinculação do Adulto (EVA) e FACES IV (*Flexibility and Cohesion Evaluation Scale*).

Muitos doentes e portadores sofreram perdas parentais e alterações do seu percurso de vida durante a infância e juventude; tinham mais sintomas psicopatológicos que a população em geral; os doentes, comparados com os assintomáticos, tinham um Índice Global de Sintomas mais elevado e mais depressão, bem como índices mais elevados nas dimensões de vinculação insegura. Ter tido mais acontecimentos negativos na infância ou juventude estava associado a níveis mais elevados de psicopatologia. Estas pessoas percecionavam o seu funcionamento familiar como equilibrado, obtendo-se níveis elevados nas escalas de coesão e flexibilidade e baixos nas escalas desequilibradas. Estes resultados eram semelhantes nos cônjuges/companheiros, corroborando os primeiros. Quando comparados com os doentes com esclerose múltipla os resultados obtidos para as escalas coesão e flexibilidade eram significativamente mais baixos, bem como os níveis de comunicação e satisfação. Poderia concluir-se que, apesar de não existirem famílias percecionadas como desequilibradas, na doença não genética estas seriam tendencialmente mais equilibradas. A comunicação era um fator a ter em conta nas famílias dos portadores, onde mais pessoas a relatavam como baixa.

Concluímos que esta é uma população mais vulnerável ao *distress* psicológico, em que as alterações psiquiátricas, nomeadamente a depressão e outros sintomas psicopatológicos podem estar presentes. A doença implica ao longo da vida vários fatores de sobrecarga psicológica e de organização emocional com impacto nos portadores e nas famílias. O apoio psicológico, individual e familiar é necessário e deve ser incluído nas equipas multidisciplinares.

ABSTRACT

ATTR amyloidosis V30M or transthyretin-related polyneuropathy (TTR-FAP) is a hereditary, late-onset, systemic amyloidosis. It is a rare disease; although existing all over the world, it has clusters of higher prevalence in the northwest of Portugal, Sweden and Japan. It is a chronic disease, with variable clinical expression dominated by a sensory-motor and autonomic neuropathy. Symptoms are generalized and include gastrointestinal, eyes, skin, kidney, heart, with early sexual dysfunction of loss of sphincters control. It progresses with marked weight loss, motor deficiency and leads to great physical incapacity. In the absence of any treatment, it evolves to loss of autonomy and death, on average, after 11 years. At advanced stages, patients become completely dependent for activities of daily life. For a long time, only symptomatic and palliative treatments were available. Currently there are some alternative treatments, but no cure.

Its devastating features, adult-onset and hereditary (autosomal dominant) nature impose a psychological burden on patients and their families. Members of these families live throughout their existence, questions of uncertainty about their carrier status, clinical diagnosis, reproductive choices and fate of close relatives.

The goals of this thesis were related to the psychopathological implications this disease may have on patients and presymptomatic carriers and their families: to study life events arising from the disease, evaluate psychopathological dimensions, understand how life-events influence psychopathological alterations, understand how adult attachment structures in these families and what is the relationship of life events with psychopathology; and to compare them with patients with multiple sclerosis (MS), also a chronic, neurodegenerative, but not hereditary disease.

Participants had the Val30Met variant (109 patients, 81 presymptomatic carriers and 81 with no established diagnosis) followed at the Corino de Andrade Unit, Hospital Centre of Porto (CHP); 41 spouses/partners; and 34 patients with MS followed at neurology consultation (CHP). In addition to a Sociodemographic Questionnaire, the Brief Symptom Inventory-53 (Portuguese version), the Adult Attachment Scale (EVA) and the Flexibility and Cohesion Evaluation Scale (FACES IV) were applied.

Many participants suffered parental losses and changes in their life course during childhood and adolescence, and had more psychopathological symptoms than the general population; patients had a higher overall symptom score and more depression, as well as higher rates of insecure attachment dimensions, when compared with presymptomatic carriers. There

was also a greater relationship in these participants with higher rates of psychopathology: more negative events during childhood or adolescence were associated with higher levels of psychopathology.

These persons perceived their family functioning as balanced, having achieved high levels on the cohesion and flexibility scales and low levels on unbalanced scales; results were similar for spouses/partners, corroborating those results. When compared with MS patients, the results in cohesion and flexibility were significantly lower, as well as the levels of communication and satisfaction. It could be concluded that although there are no families perceived as unbalanced, in MS they tended to be more balanced. Communication was an issue in these families, more people reporting it as low.

We concluded that these patients and families are more vulnerable to psychological distress, in which psychiatric changes, namely depression and other psychopathological symptoms, may be present. The disease brings about several factors of psychological overload and of emotional organization with impact in patients and in their families, throughout their lives. Psychological, individual and family support is very much needed and should be included in multidisciplinary care teams.

LISTA DAS PUBLICAÇÕES INCLUIDAS NA TESE

Na dissertação foram incluídos os resultados de artigos publicados, de manuscritos submetidos para publicação e de um estudo preliminar publicado no Proceedings Book do XIIIth International Symposium on Amyloidosis.

ESTUDO PRELIMINAR

Lopes A, Rodrigues C, Sousa A, Cunha Z, Teixeira L, Coelho T. Familial Dynamics, Attachment and Psychopathology in Familial Amyloidotic Polyneuropathy Patients. In Hazenberg BPC, Bijzet J (eds.), XIIIth International Symposium on Amyloidosis "From Misfolded Proteins to Well-Designed Treatment". Groningen (2012)

ESTUDO 1

Lopes, A., Sousa, A., Fonseca, I., Branco, M., Rodrigues, C., Coelho, T., Sequeiros, J., & Freitas, P. (2018). Life paths of patients with transthyretin-related familial amyloid polyneuropathy Val30Met: a descriptive study. *Journal of community genetics*, *9*(1), 93-99.

ESTUDO 2

Lopes A, Fonseca I, Sousa A, Branco M, Rodrigues C, Coelho T, Sequeiros J, Freitas P. Psychopathological Dimensions in Portuguese Subjects with Transthyretin Familial Amyloid Polyneuropathy. *Biomedicine Hub*. 2017; 2:485118 (DOI: 10.1159/000485118)

ESTUDO 3

Lopes, A., Fonseca, I., Sousa, A., Rodrigues, C., Branco, M., Coelho, T., ... & Freitas, P. (2018). Psychopathological dimensions in subjects with hereditary ATTR V30M amyloidosis and their relation with life events due to the disease. *Amyloid*, *25*(1), 26-36.

ESTUDO 4

Lopes A, Sousa A, Fonseca I, Branco M, Rodrigues C, Coelho T, Sequeiros J, Freitas P. Adult Attachment and Psychopathological Dimensions in Subjects with Transthyretin-Related Familial Amyloid Polyneuropathy (TTR-FAP).

Submetido para publicação (2018)

ESTUDO 5

Lopes, A., Rodrigues, C., Fonseca, I., Sousa, A., Branco, M., Coelho, T., Sequeiros, J. & Freitas, P. (2018). Family dynamics in transthyretin-related familial amyloid polyneuropathy Val30Met: Does genetic risk affect family functioning?. *Clinical genetics*.

PALAVRAS-CHAVE/KEYWORDS

Transthyretin-related familial amyloid polyneuropathy

Polineuropatia amiloidótica familiar

Amiloidose ATTR V30M

ATTR amyloidosis V30M

TTR-FAP

Ansiedade/Anxiety,

Depressão/Depression,

Sintomas psicopatológicos/Psychopathological symptoms,

Psychosocial

Psiquiatria/Psychiatry

Life events

Vinculação do adulto/ Adult attachment

AAS-R/EVA

BSI/Brief Symptom Inventory-53

Dinâmicas familiares/ Family functioning

FACES IV

LISTA DE ACRÓNIMOS

AA/VA	Adult attachment/Vinculação do adulto
AAS-R/EVA	Adult Attachment Scale/Escala de Vinculação do Adulto
BSI-53	Brief Symptom Inventory
CHP	Centro Hospitalar do Porto
DGPI	Diagnóstico genético pré-implantação
DPN	Diagnóstico pré-natal
EDSS	Expanded Disability Status Scale
EM	Esclerose múltipla
FACES	Family Adaptability and Cohesion Scale
FAP	Familial amyloid polyneuropathy
GSI	Global Severity Index
HSA	Hospital de Santo António
MS	Multiple sclerosis
PAF	Polineuropatia amiloidótica familiar
PAF-TTR	Polineuropatia amiloidótica familiar relacionada com a transtirretina
PSI	Positive Symptom Index
PST	Positive Symptom Total
SD	Standard deviation
TH	Transplante hepático
LT	Liver transplantation
TTR	Transtirretina/Transthyretin
TTR-FAP	Transthyretin-related familial amyloid polyneuropathy

CAPÍTULO 1

INTRODUÇÃO

INTRODUÇÃO

Neste capítulo será apresentada uma perspetiva geral sobre o âmbito de estudo desta dissertação. Faremos uma descrição da polineuropatia amiloidótica familiar (PAF), designação tradicional desta patologia ou, de acordo com as nomenclaturas mais atuais, amiloidose ATTR V30M ou polineuropatia amiloidótica familiar relacionada com a transtirretina V30M (PAF-TTR), bem como das questões-chave que a doença, dadas as suas caraterísticas, irá implicar.

É possível verificar ao longo desta dissertação, bem como nos artigos publicados que a consubstanciam, que a doença foi designada de várias maneiras. Polineuropatia amiloidótica familiar é a designação que está no título desta tese, aprovada há alguns anos. A evolução da designação correspondeu à evolução do conhecimento da doença. Antes e depois da submissão desta tese, a doença foi nomeada de várias formas. O nome popular, "doença dos pezinhos", ainda perdura e identifica-a facilmente no nosso país. "Paramiloidose" é a designação utilizada coloquialmente, também nos meios médicos. "Doença de Andrade", foi também outro nome que a descreveu e Corino de Andrade, no Handbook of Clinical Neurology, chamou-lhe "hereditary amyloid neuropathy" (Vinken & Bruyn, 1969). Polineuropatia amiloidótica familiar foi durante muito tempo a designação que servia a uma amiloidose sistémica com sintomas de predomínio neurológico – neuropatia periférica sensitivo-motora e autonómica. Os avanços bioquímicos e da biologia molecular permitiram reconhecer a proteína anormal (TTR) e também várias mutações para além da mais comum (V30M) que caracteriza os participantes neste estudo. Pelo que, o nome da doença foi incluindo as especificações que sobre ela se iam conhecendo. Finalmente, a sua "arrumação" nosológica como amiloidose sistémica, veio fazer "cair", pelo menos numa das nomenclaturas oficiais a referência à polineuropatia, impondo antes a designação mais geral de amiloidose, hereditária, por transtirretina com a mutação V30M (agora oficialmente designada como Val50Met).

Ainda assim, nos anos mais recentes, muitos artigos científicos têm alguma variabilidade na sua designação. Permitimo-nos também utilizar algumas dessas designações, espelhando isto, alguma dificuldade pela força do hábito, em assumir as mais recentes designações (e também mais correta), mas também sentindo que não incorreríamos em erro científico grave.

Assim, utilizaremos as designações PAF, PAF-TTR (polineuropatia amiloidótica familiar relacionada com a transtirretina) ou amiloidose ATTR V30M. Estaremos a designar sempre a mesma entidade.

Sendo a PAF uma doença crónica, de natureza genética e de início na vida adulta, e existindo poucos estudos de natureza psicossocial, dos quais será feita uma revisão, a questão das implicações psicossociais da doença será contextualizada também a partir dos trabalhos já existentes para outras doenças crónicas e, nomeadamente, hereditárias de início na idade adulta. A importância deste tópico para a pesquisa agora apresentada, os modelos teóricos que basearam as escolhas dos instrumentos usados na pesquisa (teoria da vinculação do adulto, sistemas familiares e modelo circumplexo de Olson) serão também revistos. Questões relacionadas com outros aspetos da presente investigação são também apresentadas, bem como os objetivos da tese.

1. A Polineuropatia Amiloidótica Familiar ou Amiloidose ATTR V30M

1.1. Uma Descrição da Doença

Foi em 1939 que o neurologista português Corino de Andrade observou o primeiro doente com paramiloidose, originário da Póvoa de Varzim. Corino de Andrade descreverá a doença num artigo seminal publicado na revista *Brain*, em 1952 (Andrade, 1952). Em 1960, no Hospital de Santa Maria, em Lisboa, Ribeiro do Rosário, Lobo Antunes e Fernando Barros registaram um outro foco da doença em Unhais-da-Serra. A investigação dos doentes do grupo de Lisboa e dos registados por Corino de Andrade, na qual colaborou também o geneticista alemão Becker, permitiu concluir de que as causas daquela doença eram hereditárias (Antunes, do Rosário, Barros, Silva, & Coelho, 1963; Becker, Antunes, Ribeiro do Rosario, & Barros, 1964).

Desde então, mais de 3700 doentes foram registados na Unidade de Paramiloidose do Centro Hospitalar do Porto, hoje Unidade Corino de Andrade.

A amiloidose associada à mutação TTR Val30Met, antes designada como polineuropatia amiloidótica familiar (PAF) é uma doença rara, hereditária, autossómica dominante, associada ao cromossoma 18 (Sparkes et al., 1987), de início tardio e envolvimento sistémico (Coelho, Sousa, Lourenco, & Ramalheira, 1994). Doença rara mas com grande distribuição geográfica a nível mundial, tem o seu maior foco no nordeste de Portugal (Da Silva, Sousa, Fonseca, & Coelho, 2004; Alda Sousa, 2006; C. T. Sousa A, Barros J,

Sequeiros J., 1995). A doença tem também grande expressão na Suécia e Japão (Holmgren et al., 1994; H. Koike et al., 2002; A. Sousa, Andersson, Drugge, Holmgren, & Sandgren, 1993) e, menor prevalência, em Espanha (sobretudo ilha de Maiorca), Brasil, França, Itália, Grécia, Turquia, Chipre, Estados Unidos, Finlândia e Argentina (Parman et al., 2016).

As amiloidoses são doenças que resultam da presença de depósitos da proteína amiloide no espaço extracelular de vários tecidos (Nienhuis, Bijzet, & Hazenberg, 2016). A amiloidogénese envolve precursores proteicos específicos, como a transtirretina no caso da amiloidose associada a esta proteína de transporte da hormona tiroideia e do retinol. Amiloidose sistémica e hereditária, na amiloidose ATTR V30M ocorre uma mutação na posição 30 da TTR, uma substituição do aminoácido valina pela metionina (Ando & Ueda, 2012; Benson & Kincaid, 2007; Merlini & Westermark, 2004; MJM Saraiva, 1996). A doença é provocada pela deposição sistémica da proteína mutada como depósitos insolúveis de fibrilas amiloides nos espaços endoneurais dos nervos periféricos e em diversos órgãos (M. J. Saraiva, Birken, Costa, & Goodman, 1984; Sipe et al., 2014). A proteína mutada é produzida principalmente no fígado, mas também nos plexos coroideus (sistema nervoso central) e na retina (Benson & Kincaid, 2007; Sekijima, Kelly, & Ikeda, 2008).

Apesar de existirem mais de 100 mutações associadas à transtirretina (TTR), com expressões clínicas variáveis, a mutação Val30Met é a mais prevalente a nível mundial (Connors, Lim, Prokaeva, Roskens, & Costello, 2003).

A idade de início de sintomas é altamente variável entre famílias e (embora menos) dentro da mesma família. A doença começa antes dos 40 anos em 80% dos doentes, com uma média de 32 anos. No Norte de Portugal onde a sua prevalência é muito elevada (90.3/100,000), esta idade média é ainda mais precoce (29,0 nos homens, 33,7 anos nas mulheres) (Coutinho, Martins da Silva, Lopes Lima, & Resende Barbosa, 1980; Hou, Aguilar, & Small, 2007; D. Santos et al., 2016; A. Sousa, Coelho, Barros, & Sequeiros, 1995; C. T. Sousa A, Morgado R, Coutinho P. , 1990). A penetrância é muito elevada e aproxima-se dos 100% nas áreas de maior prevalência. Foi encontrado um início mais precoce da doença na geração seguinte, principalmente nos homens, designado como fenómeno de antecipação (Lemos et al., 2014; C. T. Sousa A, Barros J, Sequeiros J., 1995; Yamamoto, Ikeda, Hanyu, Takeda, & Yanagisawa, 1998). Existem variantes de início tardio, sendo nestes casos mais curta a duração da doença e tendo apresentações clínicas diferentes (Conceição & De Carvalho, 2007; Haruki Koike et al., 2002; Jorge Sequeiros, Saraiva, Opitz, & Reynolds, 1987).

A amiloidose ATTR V30M é uma doença devastadora, de caráter progressivo, que conduz à perda de autonomia e morte em cerca de 11 anos quando os doentes não são submetidos a nenhum tratamento (A Sousa, Coelho, Morgado, & Coutinho, 1990). Embora tenha uma expressão clínica variável, o quadro é dominado por uma neuropatia sensitivo-motora e autonómica com sintomas gastrintestinais, vesicais e cardíacos (Adams et al., 2000; Adams et al., 2016; Andrade, 1952; Conceição, 2012; Planté-Bordeneuve & Said, 2011). A amiloide deposita-se também nos olhos (opacidades do vítreo, irregularidades da íris, glaucoma), podendo chegar a provocar cegueira, no coração (provocando perturbações da condução), nos rins (implicando situações que vão desde a microalbuminúria até insuficiência renal terminal) e no sistema nervoso central (Adams et al., 2016; Beirao, Matos, Beirao, Costa, & Torres, 2011; Lobato & Rocha, 2012; Maia et al., 2015). Os sintomas provocam grande incapacidade física, com défices motores e sobrecarga psicológica, com diminuição ou perda da função sexual, alterações na imagem corporal (associada à grande perda ponderal) e perda de controlo de esfíncteres. Em estádios avançados, estes doentes perdem a autonomia e tornam-se dependentes para as atividades da vida diária (Jonsen, Athlin, & Suhr, 1998).

Durante muito tempo, os doentes, portadores assintomáticos e as famílias com PAF, tiveram que viver com uma doença para a qual não existia tratamento a não ser sintomático e paliativo. Esperava-os o confronto com uma doença crónica e uma evolução catastrófica que, para muitos, era uma situação que tinham visto e vivenciado em familiares próximos e outras pessoas da sua comunidade. As caraterísticas familiares, a idade variável do início dos sintomas e grande variabilidade de expressão sintomática, a cronicidade da doença e evolução relativamente rápida e devastadora, submetem estes pacientes e as famílias afetadas a grande sobrecarga psicológica. A doença tem um grande impacto na vida mental e relacional das pessoas afetadas (Alice Lopes, 2003; Lopes & Fleming, 1996).

Tendo em conta a síntese predominantemente hepática da transtirretina, a transplantação hepática tornou-se um tratamento possível para estes pacientes a partir dos anos noventa (Ericzon et al., 2015; Monteiro, Freire, & Barroso, 2004; Suhr, Herlenius, Friman, & Ericzon, 2000). Em 2012, ficou disponível em Portugal e outros países o tafamidis, um fármaco que interfere com a deposição da proteína mutada (Adams, 2013; Coelho, Maia, et al., 2013). Estas duas novas formas de tratamento vieram diminuir a progressão da doença e aumentar a sobrevida dos doentes (Adams et al., 2016; Ericzon et al., 2015).

A pesquisa e a procura de novos fármacos mantêm-se. Diferentes mecanismos de ação são investigados, procurando impedir a deposição de amiloide, a formação dos seus

precursores ou a modificação da transcrição genética (Ando & Ueda, 2012; Berk et al., 2013; Coelho, Adams, et al., 2013).

O caráter familiar e o início tardio da doença levantam questões de variada natureza, antes e para além das implicações clínicas dela resultantes ou que a acompanham: o impacto transgeracional, a procura do diagnóstico e as escolhas reprodutivas.

1.2. Impacto transgeracional da doença: um jogo de espelhos

Sendo uma doença de natureza hereditária, a sua presença nas famílias onde é já reconhecida é uma constante, desde muito cedo, na existência destas pessoas. Por vezes, muito precocemente, vivem com progenitores doentes, limitados física e psicologicamente. Em muitos casos, os doentes tornam-se muito precocemente testemunhas do evoluir da doença nos seus familiares mais próximos (geralmente pelo menos um progenitor, mas também irmãos, avós tios ou outros) havendo por assim dizer, no seu imaginário e no imaginário familiar, uma presença persistente, fantasmática, com ela relacionada.

O conhecimento da doença na família implica que a pessoa, ainda antes de estar doente, vai tomar consciência da sua situação de risco genético e da decisão que pode tomar quanto à procura do teste genético e do *timing* para o fazer. Revendo-se na geração anterior e temendo tornar-se também ele um elemento transmissor para as gerações futuras.

A vivência da doença, desenrolar-se-ia, pois, a três tempos: a doença presenciada nos progenitores (num passado mais ou menos remoto), a doença a viver ou já presente no próprio e a doença que poderá vir a afetar (ou já afetou) os descendentes. Poderá então existir uma dimensão psicológica, muitas vezes dificilmente objetivável, que perpassa a vida destes sujeitos e destas famílias.

A possibilidade de transmitir a doença constitui uma potencial fonte de conflitos entre o desejo de parentalidade e a culpabilidade associada à sua transmissão (Fleming & Lopes, 2000).

Num trabalho de investigação antropológica, J.C. Louçã entrevistou vários pacientes e famílias, procurando averiguar relações intergeracionais dentro de famílias PAF que se interligassem com a questão da fertilidade (Louçã, 1997). O autor assinala que se por um lado o conhecimento da doença ou a possibilidade de vir a ser afetado permanecia como um peso/ameaça constante nestas pessoas, por outro, ter filhos parecia constituir uma forma de vitalidade que negava a doença e afirmava uma condição de “normalidade”.

A evolução médica e genética das últimas décadas veio trazer novos cenários em que a possibilidade de controlo sobre o diagnóstico do próprio e também sobre o diagnóstico da descendência se tornou possível, trazendo, no entanto, outras implicações psicológicas.

1.3. Procura do teste preditivo: saber ou não saber

Até 1984, o diagnóstico de paramiloidose era feito a partir dos elementos da história clínica e familiar e também pela biópsia de pele e nervo, onde eram identificados os depósitos extracelulares de substância amiloide (Benson & Kincaid, 2007).

A partir de 1984, passou a ser possível detetar por método relativamente simples a presença da proteína mutada no sangue circulante (MJ Saraiva, Alves, & Costa, 1989; M. J. Saraiva et al., 1984). O diagnóstico preditivo (ainda antes do eclodir da doença) passou pouco depois a ser possível. E desde então passou a ser possível, saber sobre o estado de portador pré-sintomático numa doença para a qual não existia ainda nenhum meio de tratamento. Esta foi uma alteração significativa na vida e opções destas pessoas: à impossibilidade de diagnóstico pré-sintomático sucedia um meio fácil e acessível. Não era tão fácil fugir, “negar” um conhecimento, por um lado perturbador, mas que poderia trazer também meios de maior controlo sobre opções existenciais.

O teste bioquímico à TTR mutante na PAF, iniciado em 1986, não pressupunha ainda uma análise à sequência genética ou marcadores genéticos dos potenciais portadores da doença. Este método de deteção da proteína mutada circulante, por vezes originador de erros diagnósticos, foi depois substituído pela deteção da alteração genética a partir do ADN das pessoas afetadas ou em risco. Só cerca de 10 anos mais tarde se consolidaria, no nosso país, esta prática da Genética Preditiva, com recurso a marcadores genéticos e orientada por um ´Protocolo de Teste Preditivo´, documento fundador, escrito por Jorge Sequeiros (J. Sequeiros, 2015; J Sequeiros et al., 2006).

Perante esta evolução dos métodos diagnósticos preditivos, e sendo a PAF uma doença de início na idade adulta, era reconhecida neste documento a necessidade de protocolar e legislar sobre o acesso ao teste genético. O aconselhamento genético e o suporte psicossocial necessário numa doença tardia e sem cura foram organizados, sendo legisladas as condições de procura e acesso ao teste preditivo através da Lei 12/2005. Portugal foi dos primeiros países em todo o mundo a ter uma lei que regulava a informação genética.

Saber antecipadamente sobre a hipótese de se poder vir a ter uma doença que é "património" genético familiar é uma experiência que tem levantado questões sobre os aspetos psicológicos que podem acompanhar este "reconhecimento" (Williams, Schutte, Holkup, Evers, & Muilenburg, 2000). Este período particular, antes e depois dos testes genéticos, geram tensões e ansiedades que têm sido estudados em vários contextos, nomeadamente na doença de Huntington, os quais constituíram um modelo próximo para a PAF-TTR (Tibben, 2007; Timman, Roos, Maat-Kievit, & Tibben, 2004). É por isso essencial que haja aconselhamento genético e uma orientação psicossocial durante a realização dos testes genéticos preditivos neste tipo de doenças.

O aconselhamento genético efetuado por uma equipa multidisciplinar é, pois, indispensável. A identificação de portadores assintomáticos, o seu acompanhamento regular e monitorização poderão permitir um diagnóstico mais precoce e tratamento, o que constituirá a chave para um melhor prognóstico para estes doentes (Obici et al., 2016).

O aconselhamento genético deve ser realizado por especialistas (médicos e não médicos), que ajudem os doentes e seus familiares a compreender as caraterísticas da doença, avaliar os riscos para aquela pessoa, compreender as opções que têm para lidar com a situação, incluindo as escolhas reprodutivas, de modo a usar a informação de que dispõem de um modo autónomo e com o mínimo de perturbação emocional. O aconselhamento genético deverá também ajudar a pessoa a lidar com a doença ou situação de portador (Biesecker & Peters, 2001).

No caso da paramiloidose, o protocolo deve ter sessões pré- e pós-teste genético, e a avaliação e suporte psicossocial devem existir sempre. Esta terá como âmbito motivações, processos de decisão e os recursos pessoais em termos de *coping*. Deve também prever riscos e reações psicológicas adversas, identificar valores e dinâmicas familiares, e reforçar redes de suporte social (J. Sequeiros, 2015).

As questões psicológicas que estão implicadas na realização do teste preditivo, têm sido estudadas e existem variados estudos publicados. Deles se dará conta adiante.

1.4. Escolhas reprodutivas

A par da procura do seu próprio diagnóstico de portador da alteração genética, a evolução das tecnologias de reprodução assistida veio permitir também o diagnóstico para a descendência, permitindo escolhas reprodutivas. Um artigo relativamente recente dava

conta da baixa utilização de recurso a diagnóstico pré-natal e diagnóstico genético pré-implantação na doença de Huntington, nos Estados Unidos (Schulman & Stern, 2015).

Em Portugal o diagnóstico pré-natal (DPN), isto é, o diagnóstico no feto para a alteração genética presente na PAF-TTR passou a ser possível, sendo desde 1995 regulamentado por lei, muito antes pois da lei atual, a interrupção da gravidez no caso de fetos afetados por mutações que implicam doenças genéticas com início tardio (J Sequeiros et al., 2006). Apesar de ser um método com implicações pesadas a nível psicológico e físico, são muitos os casais que o procuraram na expectativa de procriarem filhos não-afetados pela doença (J Sequeiros et al., 2006).

Em 1999 ficou disponível em Portugal o diagnóstico genético pré-implantação (DGPI), método que recorre à procriação medicamente assistida visando impedir a transmissão de doenças genéticas através da transferência uterina de embriões não afetados. O primeiro protocolo que contemplava a sua aplicação a portadores de PAF-TTR foi publicado em 2001 (F. Carvalho et al., 2001). Foi aprovado, em 2012, pelo Conselho Nacional para a Reprodução Medicamente Assistida, para a PAF-TTR. Esta aprovação, disponibilizou através do SNS este procedimento que tem custos elevados, tornando-o potencialmente acessível às famílias afetadas pela doença. O DGPI tornou-se assim mais um meio nas escolhas reprodutivas para casais em que um dos progenitores é afetado ou portador para PAF-TTR. Em 118 casais que tinham recorrido a este procedimento, 32% tinham resultado em gravidezes clínicas (Filipa Carvalho, 2015).

A baixa frequência de recurso ao DGPI, bem como a sua menor utilização por pessoas com mais baixo rendimento foi evidenciada num estudo numa população de sujeitos com a mutação (Valdrez, Alves, Coelho, & Silva, 2014). O método era conhecido pelos mais jovens, com maior poder económico e mais educados; evocavam-se como razões para não recorrer ao método, os custos económicos, as incertezas técnicas e o tempo para conseguir engravidar (Valdrez, Silva, Coelho, & Alves, 2014).

Os processos de decisão dos casais em relação a qualquer dos métodos são complexos e implicam dimensões de natureza cognitiva, emocional e moral. A incerteza e informação probabilística resultam em emoções conflituantes que influenciam estes processos de decisão no DGPI (Hershberger & Pierce, 2010).

Em qualquer dos contextos (DPN e DGPI), ambos os progenitores devem receber aconselhamento genético protocolado, tendo um deles de ser comprovadamente afetado ou portador pré-sintomático. No caso do DPN, o processo de aconselhamento e avaliação

psicossocial deve demonstrar uma inequívoca motivação para a interrupção da gravidez se o feto tiver a mutação.

Qualquer destas escolhas pode ter custos psicológicos associados às vicissitudes dos procedimentos. Procedimentos físicos invasivos, frustração de expectativas ou a interrupção de gravidez, no caso do DPN, com consequências psicológicas negativas (Leithner et al., 2004), implicam a necessidade de aconselhamento e acompanhamento psicológico destes casais. Os casais que procuram o DGPI têm além disso, de enfrentar tempos de espera, baixa taxa de sucesso, implicações da terapia hormonal associada, o que pode ter também consequências emocionais.

Embora existam atualmente alguns tratamentos para esta doença, os seus benefícios não se estendem a todos os doentes (têm de estar em fase inicial, alguns não respondem ao tafamidis, há rejeição de transplantes hepáticos e elevada mortalidade) e não oferecem a cura para a mesma, já que a mutação genética continua presente, pelo que o aconselhamento genético para as escolhas reprodutivas se mantém essencial.

2. Estudos Psicossociais em Doentes com amiloidose ATTR V30M

Os estudos psicossociais em sujeitos com esta mutação têm sido predominantes no contexto do aconselhamento genético e impacto do teste preditivo. Também no âmbito da transplantação hepática se realizaram estudos desta natureza.

Serão neste capítulo focados outros estudos publicados e que incluem ainda outros aspetos psicológicos relacionados com a PAF-TTR.

2.1. Estudos psicossociais e teste preditivo

Os indivíduos pertencentes a famílias em que a PAF-TTR está presente, correm o risco de vir a desenvolver a doença e o confronto com esse risco e o ter conhecimento do seu estatuto genético tem um grande impacto psicológico nas suas vidas e no seu núcleo familiar e social. Esta é, por isso, uma das áreas que tem merecido investigação e sobre a qual têm sido publicados diversos trabalhos.

Desde há muito tempo que existe uma preocupação a propósito das consequências psicológicas que pode ter o conhecimento do estado genético nos indivíduos em risco para uma doença de início tardio que procuram o teste pré-sintomático. A doença de Huntington

tem sido uma das doenças mais estudadas sob este ponto de vista, embora pessoas com outras doenças genéticas de início tardio, por exemplo a Doença de Machado Joseph, tenham sido também objeto de estudos semelhantes (Carlos Gonzalez et al., 2012; C. Gonzalez et al., 2004; Tibben, 2007; Tibben, Timman, Bannink, & Duivenvoorden, 1997; Timman et al., 2004). A informação sobre o estado genético pode constituir um risco psicossocial para o indivíduo por ser emocionalmente perturbadora, mas por outro lado, o conhecimento sobre a existência da doença, pode ajudar os indivíduos e as famílias a planearem as suas vidas, aumentando o sentimento de controlo e portanto, conter elementos emocionalmente positivos (Wiggins et al., 1992).

Por outro lado, foi observado por Schwartz (Schwartz, 2010) que há um impacto psicológico ao receber um diagnóstico genético positivo e que este tem fortes implicações em toda família. Não foram encontrados nestes sujeitos consequências graves do ponto de vista psicopatológico, a curto prazo, após a realização do teste genético (Tibben, 2007; Tibben et al., 1997). O risco mais elevado, a médio prazo, foi encontrado em sujeitos que tinham uma motivação mais baixa e inespecífica, para a realização do teste, bem como uma maior fragilidade egóica (Decruyenaere et al., 2003).

O impacto psicológico do teste pré-sintomático (TPS) para a PAF foi estudado, quer antes quer depois da sua realização. Não se encontraram consequências psicológicas graves, embora estivesse presente algum *distress* psicológico. O TPS parecia melhorar o bem-estar psicológico dos sujeitos, sendo os níveis de ansiedade e depressão prévios bons preditores desses resultados (S Lêdo, Paneque, Rocha, Leite, & Sequeiros, 2013; Paneque, 2008a; Rolim, Leite, et al., 2006). Os níveis de *distress* emocional diminuíam após 3 meses e 1 ano para portadores e não-portadores, embora nestes fosse mais expressivo (S. Lêdo, Leite, & Sequeiros, 2014). Foram encontrados índices psicopatológicos mais elevados nestes grupos do que na população em geral. O funcionamento e apoio familiares eram importantes antes e depois do teste, diminuindo o impacto psicológico do teste (Paneque, 2008b). Esta autora comparou o comportamento psicológico das pessoas em risco para a PAF com sujeitos em risco para ataxia cerebelosa tipo 2, e identificou fatores na PAF que podiam diminuir a resposta psicológica perturbada ao TPS: a experiência prévia da doença na família, a maior proximidade relacional com o familiar afetado, o fato de ser a mãe a transmissora e finalmente, o equilíbrio emocional prévio (Paneque et al., 2009).

Estudos a médio e longo prazo após o TPS, evidenciaram que a depressão e ansiedade variavam nos sujeitos: a depressão ocorria quando os sujeitos tinham manifestado os primeiros sintomas enquanto a ansiedade estava presente quando se aproximava a idade

de início da doença (Ledo, Leite, Souto, Dinis, & Sequeiros, 2016; S. Lêdo, Leite, Souto, Dinis, & Sequeiros, 2016; Susana Lêdo, Leite, Souto, Dinis, & Sequeiros, 2017).

Portanto, embora se possa dizer que a possibilidade da existência de algum *distress* psicológico esteja ligado à realização e reconhecimento pelo sujeito do seu estado genético, os estudos apontam, na grande maioria dos sujeitos, para situações não muito graves do ponto de vista psicopatológico.

Não saber sobre o estado genético tem de ser também considerada uma possibilidade. A propósito da análise de casos clínicos foram evidenciados a enorme luta e possível conflito que podem estar ligados a este conhecimento, que contém também o conhecimento/incerteza face à descendência ou a culpabilidade inerente (Fleming & Lopes, 2000).

No entanto, podemos concluir que, embora seja absolutamente necessário um enquadramento protocolar e regulamentado para a realização do TPS onde esteja obrigatoriamente contemplado o apoio psicossocial (Obici et al., 2016; Jorge Sequeiros et al., 2012), as vantagens atuais do reconhecimento do estado genético dos sujeitos pertencentes a famílias com a mutação e por isso em risco, é altamente recomendável. As vantagens do acesso à informação e tomada de consciência sobre a doença, o acompanhamento pré-início da mesma e a possibilidade de atempadamente ser considerada uma das hipóteses de tratamento são, sem dúvida, algumas das possíveis vantagens. Outras serão as que estão relacionadas com a diminuição da incerteza e possibilidade de controlo existencial. Mesmo que a incerteza, a angústia e *distress* psicológico possam continuar a estar presentes.

2.2. Estudos psicossociais na transplantação hepática

O transplante hepático (TH) constituiu na vida dos sujeitos com paramiloidose uma expectativa de futuro até aí inexistente. “Uma luz ao fundo do túnel”, como alguns doentes exprimiram, um túnel até aí conducente, inexoravelmente, a um fim anunciado e devastador. O TH trouxe, no entanto, também várias questões com implicações psicológicas e emocionais. É um procedimento cirúrgico complexo com mortalidade elevada e morbilidade associada e é um procedimento dependente da disponibilidade de órgãos, sempre de caráter aleatório e contingencial. Aguardar em lista de espera por um órgão, por vezes durante anos, constituiu para alguns doentes uma dura espera, que por vezes foi frustrada sem que um órgão tivesse chegado a tempo. O *stress* associado à toma crónica de imunossupressores, ao medo de rejeição do órgão, por vezes a necessidade de

retransplante, são outros fatores contributivos para uma maior vulnerabilidade psicológica. É, pois, natural que estudos psicossociais se tivessem realizado nesta área embora não fossem em grande número. Desde há muito que as implicações psicológicas que o TH impõe são consideradas relevantes e têm sido estudadas (Blanch et al., 2004; Nickel, Wunsch, Egle, Lohse, & Otto, 2002). Telles-Correia comparou a qualidade de vida mental após o transplante em doentes com vários diagnósticos e concluiu que aquela melhorava em várias doenças hepáticas, mas que piorava nos doentes com PAF. O mesmo autor não encontrou diferenças em relação aos diagnósticos psiquiátricos quando comparou doentes com PAF e doentes alcoólicos em lista de espera para o TH (Telles-Correia et al., 2008; Telles-Correia, Cortez-Pinto, Barbosa, Mega, & Monteiro, 2009).

Estudos fenomenológicos descreveram a experiência do transplante hepático em doentes suecos portadores da mutação. Concluíram que estes relatavam aspetos positivos e negativos ligados a essa vivência: por um lado, a ameaça de uma fatalidade inexorável tinha desaparecido, mas por outro, permanecia o sentimento de que a doença continuava apesar do transplante (os sintomas mantinham-se e os doentes permaneciam incapacitados) (Jonsen et al., 1998; Jonsén, Athlin, & Suhr, 2000). As necessidades de apoio psicossocial eram reconhecidas.

Um estudo com pacientes holandeses evidenciou que, antes e 4 anos após o TH, os pacientes com paramiloidose apesar de estarem mais deteriorados do que os que tinham outros diagnósticos, em todos os domínios físicos da qualidade de vida, eram semelhantes para o domínio emocional e saúde mental autoavaliada (Drent, Graveland, Hazenberg, & Haagsma, 2009).

O TH foi considerado como muito positivo pelos doentes transplantados, com PAF e os índices psicopatológicos eram mais baixos após o transplante, nomeadamente a depressão e a somatização (Lopes et al., 1999). Quando comparados com outros doentes transplantados por outras patologias, os níveis de Qualidade de Vida eram semelhantes. (Lopes et al., 2006). Após cinco anos de TH, porém, os doentes com paramiloidose apresentavam níveis mais elevados de depressão. Neste mesmo estudo, concluía-se que o TH tinha alterado, de forma radical, as perspetivas dos doentes quanto ao futuro, tendo um impacto psicológico muito positivo, embora pudesse ser suscetível também de determinar momentos de angústia e incerteza.

2.3. Outros Estudos Psicossociais

Apesar de os portadores da mutação relatarem de forma consistente o medo da estigmatização ligado à sua doença hereditária (Paneque et al., 2009; Rolim, Zagalo-Cardoso, Paul, Sequeiros, & Fleming, 2006), este tema só recentemente foi abordado de forma sistemática.

A PAF foi descrita como fonte de desvalorização social e de exclusão, num estudo cujo objetivo era avaliar a estigmatização sentida por doentes que viviam numa comunidade portuguesa em que a doença era altamente prevalente (Mendes, Sousa, Sequeiros, & Clarke, 2017). O reconhecimento das famílias com a doença era vivido como causador de rejeição social para os relacionamentos afetivos e desvalorizador da capacidade reprodutiva. Falar sobre a doença era sentido como muito difícil e os sujeitos sofriam uma retração social. No entanto alguns participantes referiram uma mudança importante, sentindo que a sua aceitação social era agora bastante melhor.

Num trabalho académico de investigação antropológica (Louçã, 1997), o autor entrevistou doentes e seus familiares no seu meio natural e assinalou várias questões que surgiam: a doença como "pertença" ao lado mais obscuro da memória coletiva, o facto de os membros afetados terem menor esperança de vida, o caráter incapacitante, prolongado, que colocava os doentes numa efetiva dependência de terceiros. Estes sentiam-se e eram vistos como "menos capazes para o trabalho" e "menos capazes de se reproduzirem". Sendo o controlo da natalidade, então, o único meio de controlar a doença, estes doentes tinham mais filhos o que parecia ir contra o senso comum. O autor levantava a hipótese de que ter filhos era uma forma de vitalidade que negava a doença e afirmava a condição de "normalidade" perante a comunidade, ultrapassando dessa forma o estigma associado à doença.

As representações da doença foram estudadas em sujeitos que estavam em processo de *screening* genético (Leite, Dinis, Sequeiros, & Paúl, 2016). A família aparecia como "espelho" e fonte de aprendizagem dos sujeitos, confundindo-se com a doença numa mesma representação. As narrativas dos sujeitos continham referências permanentes à família e aos familiares mais chegados. A doença era a "ameaça" portadora de luto e tristeza e de inevitável degradação física. O conhecimento objetivo da doença foi também avaliado em sujeitos em risco genético para a doença e que prosseguiam protocolo genético. A doença, o seu significado e os familiares doentes tinham um papel fundamental no conhecimento objetivo que estes sujeitos tinham acerca da PAF (Leite, Leite, & Dinis, 2017).

O impacto do risco genético para a doença sobre a angústia de morte e a imortalidade simbólica (o desejo de ultrapassar a angústia da morte pela realização de um sentido de transcendência que ajude a encarar a finitude), foi estudado (P. I. Santos, Figueiredo, Gomes, & Sequeiros, 2010). Os autores concluíram que os sujeitos em risco tinham maior angústia de morte e que essa situação ameaçava o seu sentido de imortalidade simbólica e bem-estar emocional. Advertiam para a necessidade de o aconselhamento genético incluir as questões relacionadas com a morte e para a familiarização dos profissionais com estes conceitos, para que eles pudessem ser abordados no aconselhamento genético. Esta poderia ser uma maneira de diminuir a negação associada à angústia de morte.

Alterações psicopatológicas em doentes com PAF foram descritas numa amostra de 30 sujeitos que frequentavam a consulta de psiquiatria na Unidade Clínica de Paramiloidose do Centro Hospitalar do Porto (A. Lopes, 2003; Lopes & Fleming, 1996). A ansiedade e a depressão eram os diagnósticos mais frequentes nesta população. Os sujeitos que procuravam a consulta enfrentavam também, na sua maioria, momentos de mudança no decurso da sua doença: desencadeamento da doença, altura da realização do TPS, decisão e realização do TH. A avaliação psicológica destes doentes foi também feita com a utilização do teste de Rorschach (teste psicológico projetivo). Os aspetos psicológicos dominantes eram a dificuldade de expressão emocional, sentimentos de desvalorização e baixa autoestima, sendo o medo predominante o da perda de autonomia. Os mecanismos de defesa psicológicos mais comuns eram a negação e a somatização (Alice Lopes, 2003; Lopes & Fleming, 1996).

No decurso da minha prática clínica com mais de 20 anos de psiquiatria com estes sujeitos, portadores sintomáticos e também assintomáticos ou simplesmente ainda em risco genético, os diagnósticos psicopatológicos têm-se mantido constantes. Para além da patologia depressiva e ansiosa de caráter adaptativo, outros diagnósticos psiquiátricos têm sido feitos numa percentagem muito baixa (Lopes, 2006).

Parece patente, perante esta revisão, que embora breve é significativa do que se tem publicado nas áreas psicossociais e psiquiátricas da Amiloidose ATTR V30M, que muito há ainda para ser estudado nestes sujeitos.

Não existem, no nosso conhecimento, em revistas ou publicações indexadas, outros trabalhos referentes à área em questão.

Tivemos acesso a publicações académicas (teses de mestrado) que embora tendo esta temática, não acrescentavam conhecimento para além do já aqui referido, pelo que não são mencionadas.

Sabemos que para além de esta ser uma doença crónica, sem cura e durante muitos anos sem tratamento, além de sintomático e paliativo, as características hereditárias da PAF e o seu início tardio, na idade adulta, poderão amplificar o seu impacto psicológico individual e familiar.

Sabemos também que, ao longo da vida dos doentes e das famílias, são inúmeros os momentos em que potenciais desequilíbrios emocionais se podem instalar. Dúvidas, perdas e incerteza estão presentes de forma continuada na existência das pessoas com PAF e nos seus familiares. Estas serão áreas a necessitar de estudos posteriores.

3. As Doenças Crónicas e as Doenças Crónicas Hereditárias: Impacto Psicossocial no Sujeito e na Família

A PAF é uma doença crónica com evolução progressiva e devastadora. Os estudos sobre as complicações psiquiátricas e psicológicas nesta doença são escassos.

É sabido, no entanto, por inúmeros trabalhos de pesquisa, que as doenças crónicas têm importantes consequências psiquiátricas e psicossociais. Pretende-se aqui compreender a partir desses estudos de que modo isso acontece nas doenças crónicas e, mais especificamente, também nas doenças crónicas hereditárias.

Estas patologias representam ameaças e desafios permanentes que implicam processos psicológicos adaptativos exigentes. Impõem dúvidas diagnósticas e incertezas, perdas de várias naturezas, funcionais, de qualidade de vida e de autonomia assim como incertezas quanto ao futuro, o qual poderá trazer mudanças individuais, sociais e familiares (Charlotte Delmar et al., 2006).

A doença crónica em geral e a doença neurológica em particular têm sido associadas a depressão, ansiedade e *distress* psicológico. A comorbilidade psiquiátrica está associada a pior prognóstico com aumento da morbilidade e mortalidade em doenças cardíacas, neurológicas, autoimunes, oncológicas, na doença vascular cerebral, nas doenças neuromusculares e reumatológicas, para citar algumas (Cohen, Norris, Acquaviva, Peterson, & Kimmel, 2007; Dale, Maltby, Shimozaki, Cramp, & Rickards, 2016; Devins, 2006; Frasure-Smith, Lesperance, & Talajic, 1995; W. Katon, Lin, & Kroenke, 2007; W. J. Katon, 2011; Loubinoux et al., 2012; Siegert & Abernethy, 2005; Walklet, Muse, Meyrick, & Moss, 2016; Zuidersma, Thombs, & de Jonge, 2011).

As consequências da doença crónica sobre as famílias manifestam-se nas possíveis alterações de padrões de vida devidas a perdas económicas, sociais e lutos (Breier et al., 1988).

Num estudo de revisão (Golics, Basra, Finlay, & Salek, 2013), era assinalado que o impacto da doença nas famílias e na sua qualidade de vida era ainda bastante desconhecido e subestimado. A autora referia que a dificuldade de avaliação se prendia possivelmente, com a inexistência de instrumentos apropriados, que eram na sua maior parte muito específicos para cada patologia.

A doença e a sua história na família podem provocar acontecimentos traumáticos, nomeadamente nos elementos mais jovens, por exemplo a perda parental (McLaughlin et al., 2012; Tyrka, Wier, Price, Ross, & Carpenter, 2008), com consequências psicopatológicas significativas a curto e a longo prazo.

Problemas de disfunção familiar e problemas psicológicos nos filhos foram encontrados em famílias em que um dos progenitores sofria de uma doença crónica (Bogosian, Moss-Morris, & Hadwin, 2010; Steck et al., 2007). Razaz (Razaz et al., 2016) avaliou os filhos de doentes com esclerose múltipla e verificou que a depressão dos progenitores e o *stress* parental eram *stressores* que tinham implicações na sua vida mental. Num grupo de famílias em que um dos progenitores tinha doença de Huntington, havia alterações da capacidade parental dos dois progenitores, quer do afetado como do não afetado (Vamos, Hambridge, Edwards, & Conaghan, 2007).

Na literatura têm sido consideradas também as importantes consequências psicológicas que as doenças crónicas implicam para os cuidadores mais próximos (Lim & Zebrack, 2004), os quais muitas vezes são eles próprios familiares em risco e sujeitos a diversos tipos de sobrecarga emocional e psicossocial.

A perspetiva que aqui queremos agora evidenciar prende-se com a experiência da doença genética na família e de como tem sido descrita na literatura, tendo em consideração o sistema familiar (Brouwer-DudokdeWit, Savenije, Zoeteweij, Maat-Kievit, & Tibben, 2002; Sobel & Cowan, 2003).

Esta abordagem específica para a compreensão dos desafios psicossociais das famílias com doença crónica genética foi proposta por Street e Soldan (Street & Soldan, 1998). Tendo como base o modelo de Rolland, “family systems illness”, para a doença crónica em geral, em que eram previstos três estádios fundamentais na doença crónica (crise inicial, curso e adaptação e fase terminal), aqueles autores propuseram outros componentes para a inclusão da doença genética. Para além da tipologia psicossocial associada à doença

crónica, a consideração no tempo das fases de uma doença ou condição genética e a perspetiva sistémica com o enquadramento no ciclo de vida familiar tal como Rolland havia proposto para a doença crónica. Incluíam, deste modo, a fase pré doença de uma condição genética e a situação de portador genético, que Timmermans viria a chamar "pacientes à espera" (Timmermans & Buchbinder, 2010). Esta nova fase, propiciada pela disponibilização em muitas doenças genéticas de testes preditivos, veio carregada de incertezas que lhe eram inerentes dado o desconhecimento da altura de início da doença. Ela viria também tornar mais ténue a diferença entre saúde e doença.

Mais tarde, Rolland e Williams alargariam o seu próprio modelo incorporando as questões próprias das doenças genéticas (FSGI - family systems genetic illness) (John S Rolland & Williams, 2005). Incluindo as fases pré-sintomáticas bem como as fases pré-diagnóstico, incorporavam os impactos próprios delas, e a consideração dos processos de *coping* com que os vários membros da família estavam confrontados. O conhecimento do risco genético, a consideração dos processos de decisão em relação ao TP, a necessidade de informação do próprio e dentro da família, constituem sem dúvida, dificuldades com que estes sujeitos têm de se confrontar. De acordo com o ciclo de vida familiar estes sujeitos são levados a fazer escolhas (por exemplo, reprodutivas) que trarão também algum impacto psicossocial. De acordo com o modelo de Rolland, a PAF seria classificada como uma doença genética grave com idade de início tardia, sem cura embora com tratamentos já disponíveis.

Podemos também concluir, o que já antes já tínhamos percebido pela clínica: que existem momentos particularmente vulneráveis na vida destes sujeitos e destas famílias que se prendem com a evolução e mudança de situação no próprio e/ou no sistema familiar relacionadas com a doença.

Este é um modelo compreensivo não quantificável, que não tem instrumentos de medida. No entanto, permite-nos sem dúvida uma compreensão abrangente destas pessoas e destas famílias. Este modelo sustenta, teoricamente, a necessidade de estudar nestas pessoas vários aspetos psicossociais. Em primeiro lugar, estudar aspetos ligados às consequências psicológicas/psiquiátricas da doença no próprio, e também da sua vivência ainda antes de a doença ser reconhecida e/ou diagnosticada. Depois, estudar as consequências da doença, nomeadamente, no modo como afeta o sistema familiar em várias fases do seu ciclo. E, finalmente, sendo o sistema familiar considerado como um todo, a base e âmbito de alguns destes estudos, ele também e o seu funcionamento deveriam ser considerados como objeto do presente trabalho.

A descrição da doença, das suas características e vicissitudes ao longo da existência dos sujeitos afetados e das famílias, o que sabemos acerca de outras doenças crónicas e genéticas com características semelhantes à paramiloidose e, também, não podemos deixar de o dizer, a nossa experiência clínica ao longo de vinte anos, vieram levantar-nos perguntas para responder.

Sendo a doença em muitas famílias presente e reconhecida por mais de uma geração, quantos destes sujeitos experienciam/sofrem acontecimentos de vida relacionados com a ela (doença ou a morte dum progenitor, por exemplo) durante os primeiros anos da sua vida? Qual a importância destas ocorrências nestas populações?

Temos encontrado, em muitos dos doentes que nos procuram na consulta de psiquiatria, histórias de perdas parentais, de lutos adiados, de experiências de parentificação. Mas o que não sabíamos era até que ponto estas alterações existenciais seriam ou não frequentes e importantes nestas famílias. Por outro lado, não sabíamos também de que modo a doença, nomeadamente a doença num progenitor, altera ou perturba o desenrolar existencial da vida destes sujeitos e das famílias; e se estas alterações seriam também geradoras de alterações psicológicas/psicopatológicas.

Por outro lado, que consequências psicopatológicas traz a doença para estas pessoas e para os seus familiares? E qual a importância que poderá ter na psicopatologia destes sujeitos, a exposição a perdas e lutos precoces, tal como tem sido descrito na literatura para outras situações?

Esta questão fez-nos também pensar nas consequências que poderiam existir, dadas as perdas precoces, para as suas caraterísticas de vinculação, o que nos propusemos responder.

Finalmente, sendo esta uma doença familiar e a família o centro onde tudo decorre e onde tudo flui (informação ou desinformação, emoções expostas ou negadas, transmissão genética e de crenças e atitudes) interrogamo-nos como estas famílias se organizariam, se o funcionamento familiar teria características mais ou menos saudáveis, funcionais ou disfuncionais, que pudessem ser relacionadas com a presença da doença genética.

Propusemo-nos assim, estudar nos portadores sintomáticos e assintomáticos de amiloidose ATTR V30M, as consequências psicopatológicas da doença na idade adulta, e também mudanças psicossociais percecionadas no passado, decorrentes da presença da doença, e como estas se poderiam exprimir na vida atual do doente, nomeadamente em termos psicopatológicos, de estilos de relações interpessoais e das características das dinâmicas familiares.

Para estudar aspetos psicológicos que podem ter implicações psicopatológicas e no modo como estes sujeitos estabelecem relações interpessoais e lidam com a doença, escolhemos como suporte teórico a teoria da vinculação do adulto.

Para o estudo das dinâmicas familiares, escolhemos como suporte teórico o modelo circumplexo de sistemas familiares,

Destes modelos damos uma breve conta.

4. A Teoria da Vinculação

Foi Bowlby quem propôs a teoria da vinculação, a qual estabelece que os bebés humanos têm uma necessidade instinctual e uma capacidade inata para procurar e estabelecer proximidade e laços emocionais com uma figura cuidadora (Ainsworth & Bowlby, 1991; Bowlby, 1988; Bretherton, 1994). A partir destas interações, desenvolvem-se na criança constructos internos, de natureza afetiva e cognitiva, representações do mundo externo e das figuras significativas nele existentes. Estas representações internas estarão presentes ao longo da vida dos indivíduos e constituem o fundamento da vinculação. O sistema de vinculação de cada indivíduo é um mecanismo de sobrevivência e ficará ativo em situações de perigo ou vulnerabilidade (Bowlby, 1988).

A vinculação será segura quando o cuidador (mãe, pai ou outra pessoa) responder adequadamente às necessidades da criança. Se isto não ocorrer e as necessidades não forem satisfeitas, a vinculação será insegura. Isto poderá provocar uma maior vulnerabilidade emocional mais tarde, tendo em conta as relações com os outros. Bowlby advertiu para o caráter dinâmico e evolutivo ao logo do tempo do estilo de vinculação (Bowlby, 1988).

Também os adultos continuam a depender das relações íntimas que estabelecem com pessoas próximas para enfrentarem situações de maior perigo e vulnerabilidade emocional. A vinculação do adulto define-se como a ligação emocional a outra pessoa, que é insubstituível, embora mais do que uma pessoa possa ter esta função (Bartholomew & Shaver, 1998; Daniel, 2006). Foram definidos estilos de vinculação (seguro e inseguros) que caracterizariam a pessoa adulta e o seu modo de estabelecer relações interpessoais. Embora se tenham evidenciado elementos de congruência entre a vinculação infantil e a vinculação do adulto, nomeadamente em relação a características emocionais e comportamentais, salientaram-se algumas diferenças (Crowell & Treboux, 1995)

A vinculação do adulto (VA) e o modo como se relaciona com a vinculação precoce, com a psicopatologia, como se expressa na capacidade para a intimidade nas relações românticas, tem sido objeto de muitos estudos (van IJzendoorn & Bakermans-Kranenburg, 1996), (Davila, Ramsay, Stroud, & Steinberg, 2005; Hankin, Kassel, & Abela, 2005), (Hazan & Shaver, 1987). Estudos sobre a maneira como a VA poderia relacionar-se com expressão sintomática em doentes com doenças físicas, e influenciar a relação médico-doente interessaram-nos especialmente (Barbosa et al., 2010; McWilliams & Bailey, 2010; McWilliams, Cox, & Enns, 2000). Nestas situações, estilos de vinculação insegura estariam ligados a um aumento de sintomas médicos e a dificuldades de pedido de ajuda, com relações médico/doente mais difíceis.

A VA foi também estudada em doentes com doença de Huntington. Os autores usaram a Entrevista de Vinculação do Adulto e concluíram que estes pacientes tinham representações de vinculação segura em menor percentagem e mais representações inseguras (não resolvidas/desorganizadas) em pessoas com menos de 18 anos quando o progenitor doente tinha morrido (Van der Meer et al., 2006).

Sabe-se que a função parental pode ser afetada pela presença de uma doença crónica no progenitor ou pela depressão ou *stress* emocional nele causado (Dekkers, 2001; C. Delmar et al., 2005), o que pode provocar uma menor disponibilidade (Barkmann, Romer, Watson, & Schulte-Markwort, 2007; Boss & Couden, 2002), com implicações nas relações com os filhos e eventualmente no desenvolvimento dos padrões de vinculação.

Os comportamentos de vinculação são ativados em situações que comportam ameaça e desafio para o sujeito. As doenças, tendo habitualmente estas características, desencadearão tais comportamentos que deverão ser compreendidos pelos profissionais de saúde, quer resultem de estilos seguros e adequados (necessidade de proximidade, protesto face a separações e procura de uma base segura), quer de estilos inseguros em que o evitamento ou o medo/angústia de ser abandonado e, portanto, a procura de uma dependência excessiva possam ser predominantes (Cookman, 2005).

Tendo estabelecido o nosso interesse pelo estudo da VA nos doentes com PAF, tivemos que escolher os instrumentos para essa avaliação. Embora a Entrevista de Vinculação do Adulto de Crowel e Treboux (1995) (Crowell & Treboux, 1995; George, Kaplan, & Main, 1996) pudesse trazer mais informação de carácter dinâmico, relacionando os resultados atuais com a vinculação infantil e o passado dos sujeitos avaliados, optamos pela utilização da Escala de Vinculação do Adulto de Collins e Feeney (2000) (Collins & Feeney, 2000), uma escala de autoavaliação, quantitativa, que apresentava maior exequibilidade para o projeto atual.

5. Dinâmicas Familiares e Modelo Circumplexo

A família, definida por Aristóteles como unidade básica social e, por Rousseau, como a única instituição natural através dos tempos, mantém apesar de inúmeras "atualizações" e mudanças, a sua importância social primordial. As funções essenciais do sistema familiar, de acordo com Schwab (Schwab, Gray-Ice, & Prentice, 2006) seriam a manutenção do grupo, a sua perpetuação, a regulação da sexualidade dos adultos, a provisão de suporte emocional para os membros da família, e a aprendizagem e aculturação de valores, crenças e capacidades.

A família, principal motor para o desenvolvimento pessoal dos seus membros, possibilita o seu crescimento e autonomização, com a criação ao mesmo tempo de um sentimento de pertença (Relvas & Alarcão, 2002). Sendo o comportamento de cada um dos membros da família indissociável dos restantes, aquilo que acontece individualmente afetará a família no seu conjunto (Alarcão, 2002).

A história da família não é sempre linear nem causal e ela constitui-se como lugar de múltiplas vinculações, continente securizante, mas também por vezes inibidor, inseguro e vulnerabilizante (Delage & Cyrulnik, 2010). Estes autores propõem a existência de uma resiliência familiar que face ao trauma vivido na família, poria em marcha mecanismos de regulação da vida emocional, com trocas e comunicação tendentes a manter a funcionalidade.

A questão da família, como elemento central na patologia de que nos ocupamos, bem como de igual modo noutras patologias de natureza hereditária e de início tardio, é um facto de primordial importância, que não parece carecer de demonstração.

Assim, para o estudo destas famílias, para compreender o seu funcionamento, era necessário fazer uma opção metodológica.

As opções para o estudo das famílias são diversas e sempre complexas. O sistema familiar é um sistema complexo, dinâmico e em mudança permanente e a sua avaliação, nomeadamente quantitativa, levanta muitas questões e críticas possíveis (Wampler & Halverson, 1993). Estas avaliações, para além do mais, podem provir de várias fontes, de um observador externo ou de elementos da própria família por autoavaliação, podendo ser ou não convergentes e podem ter como objeto as relações pais-filhos, o casal ou a família como uma unidade. A necessidade de recurso a métodos quantitativos, embora podendo

ser redutora, pode ser explicada pela necessidade de comparação entre grupos (Wampler & Halverson, 1993).

Porque a família como sistema tem sido a base de muitos estudos em situações de doença crónica, genética, e também por afiliação pessoal ao modelo teórico, optamos por estudar a família como uma unidade sistémica e utilizar como suporte teórico o Modelo Circumplexo de Sistemas Maritais e Familiares.

O modelo sistémico encara a família como um todo orgânico, um sistema de interações, em constante transformação adaptando-se a diversas fases do seu ciclo de desenvolvimento (Andolfi, 2012).

O Modelo Circumplexo de Sistemas Maritais e Familiares é um modelo resultante da teoria sistémica familiar que tem sido usado com fins clínicos e terapêuticos e também como base teórica investigacional. Foi desenvolvido por Olson, Portner e Lavee, em 1974 e descreve o funcionamento familiar usando três conceitos básicos, *coesão, flexibilidade* e *comunicação,* que resultaram de uma revisão de conceitos utilizados por diferentes autores para descrever os casais e as dinâmicas familiares (DH Olson, Portner, & Lavee, 1985; D. H. Olson, 2000; D. H. Olson, Sprenkle, & Russell, 1979).

A coesão é definida como a ligação emocional que os membros da família têm uns com os outros e é classificada como desligada, separada, ligada (coesa) ou emaranhada (DH Olson et al., 1985). A flexibilidade é definida como a qualidade e expressão de liderança e organização, de regras relacionais e de negociações (David Olson, 2011). É categorizada como caótica, flexível, estruturada e rígida (DH Olson et al., 1985).

A comunicação é definida como as capacidades de comunicação positiva usadas pelo casal e pelo sistema familiar (David Olson, 2011). Níveis elevados de comunicação nas famílias são conducentes a mudanças que favorecem a coesão e flexibilidade.

O Modelo Circumplexo é a base teórica da escala de avaliação da FACES (Family Adaptability and Choesion Scale), agora na sua quarta versão, FACES IV. Esta versão resultou do desenvolvimento de quatro escalas desequilibradas relacionadas com os valores extremos das dimensões coesão (emaranhado e disperso) e flexibilidade (rígido e caótico), que permitiram uma melhor discriminação entre famílias problemáticas e não problemáticas (David Olson, 2011). A hipótese deste modelo estabelece que níveis equilibrados de coesão e flexibilidade (baixos a altos) conduzem a um funcionamento familiar saudável, enquanto níveis desequilibrados de coesão e flexibilidade estão associados a funcionamento familiar mais problemático.

6. Objetivos

As finalidades gerais deste trabalho prenderam-se com a procura de mais conhecimento sobre dimensões de âmbito psicossocial, nomeadamente psicopatológicas, nos doentes e portadores da mutação para a paramiloidose, TTR V30M. A procura de sistematizar observações empíricas que nos remetiam para a hipótese de uma existência individual e familiar marcada fortemente pela doença, pelas ocorrências a ela ligadas (morte, doença e limitações, mudanças sociais e individuais) levaram-nos por outro lado, a estabelecer objetivos que pelo menos em parte respondessem também a essas questões. Por outro lado, a família, elemento central e sempre presente na vida destes sujeitos, ligada a todos os aspetos anteriores, impunha-se também como objeto de estudo.

As finalidades específicas do presente trabalho foram:

1. Estudar os acontecimentos de vida decorrentes da doença e a perceção tida por eles em portadores sintomáticos e assintomáticos da mutação PAF-TTR Val30Met.

2. Avaliar as dimensões psicopatológicas nos portadores sintomáticos e assintomáticos da mutação Val30Met.

3. Analisar de que modo os acontecimentos de vida decorrentes da doença e da evolução da mesma influenciavam as alterações psicopatológicas; e se estas eram mais evidentes nos que tinham referenciado acontecimentos de vida decorrentes da doença.

4. Perceber de que modo a vinculação do adulto se estruturava nesta população; se esta podia relacionar-se com a doença, com os acontecimentos de vida dela decorrentes, tal como eram percecionados pelos participantes no estudo; e qual a sua associação com dimensões psicopatológicas

5. Analisar a dinâmica familiar percecionada pelos portadores sintomáticos e assintomáticos da mutação PAF-TTR V30M, as caraterísticas e funcionalidade destas famílias; assim como a dinâmica familiar percecionada pelos seus cônjuges.

6. Comparar as caraterísticas e funcionalidade das famílias com PAF com famílias de doentes com esclerose múltipla (patologia neurológica crónica, degenerativa, evolutiva, mas não hereditária).

CAPÍTULO 2

MÉTODOS GERAIS

MÉTODOS GERAIS

1. Desenho do Estudo

Para a prossecução dos objetivos desta tese foram realizados 6 estudos, sendo o primeiro identificado como um estudo preliminar. Partilha com o estudo 4 objetivos semelhantes, embora tenham amostras diversas e algumas diferenças de metodologia explicitadas nos resultados (Cap. 3). Esse estudo preliminar foi, de certa forma, desencadeador e estruturante dos outros estudos inseridos nesta tese.

2. Amostra

Os participantes nos estudos eram regularmente seguidos na consulta externa da Unidade Corino de Andrade, do Centro Hospitalar do Porto. Todos eram positivos para a mutação Val30Met na TTR, sintomáticos (n=109), assintomáticos (n=81) e alguns não tinham ainda diagnóstico clínico estabelecido da doença (n=19). Um grupo de cônjuges (n=41) foi convidado a participar no estudo, para responder a parte do objetivo 5. Um grupo adicional de 34 doentes com esclerose múltipla foi recrutado para responder ao objetivo 6.

Os portadores de amiloidose ATTR V30M, sintomáticos e assintomáticos, foram recrutados entre 2013 e 2015 aquando da sua consulta de rotina naquela instituição e foi-lhes proposta a sua participação voluntária nos estudos.

Os cônjuges que responderam aos questionários, foram convidados pessoalmente a participar no estudo quando acompanhavam os portadores da mutação à consulta de rotina na Unidade Corino de Andrade.

Os doentes com esclerose múltipla foram recrutados durante a sua consulta de rotina que se realiza também na Unidade Corino de Andrade.

Foram considerados elegíveis os sujeitos que tivessem entre 18 e 65 anos.

As amostras dos diferentes estudos tiveram tamanhos diferentes, com base no preenchimento de questionários que se foram realizando, diferenças que passamos a explicitar.

Os estudos 1, 2 e 3 tiveram por base a mesma amostra: 190 participantes, portadores da variante Val30Met, assintomáticos ou sintomáticos e 19 sem diagnóstico ainda estabelecido, num total de 209 sujeitos.

O grupo de participantes sem diagnóstico estabelecido é, tal como os restantes, regularmente seguido na Unidade Corino de Andrade, mas não tinham ainda um estado definido de terem já iniciado a doença. Podiam ter sintomas confundidores e não ter biopsias com deposição de amiloide ou terem biopsias com amiloide, mas não sintomas. Foram incluídos já que essa sua situação não estava diretamente implicada para os objetivos destes estudos, sendo que partilhavam todos os aspetos psicossociais implicados no facto de serem portadores da variante genética. Na verdade, a sua situação de incerteza poderia até ter mais implicações nas consequências psicossociais, principalmente a nível das dimensões psicopatológicas, embora comparações com significado estatístico não pudessem ser feitas por serem em número reduzido.

O estudo 4 teve uma amostra de 129 portadores, sintomáticos e assintomáticos com a mutação, recrutados nas circunstâncias já anteriormente consideradas. Tendo havido alguns protocolos não devidamente preenchidos, estes não foram considerados; não foram também incluídos os sujeitos duvidosos que constituíam um grupo ainda mais pequeno, por isso tornando mais difícil ou impossível o seu tratamento estatístico.

O estudo 5 teve uma amostra constituída por 115 portadores sintomáticos e assintomáticos de PAF-TTR, 41 cônjuges e 34 doentes com esclerose múltipla. Uma amostra emparelhada foi feita para comparar este último grupo com os portadores sintomáticos e assintomáticos de PAF-TTR.

O estudo preliminar foi realizado em 2011. Teve uma amostra constituída por 30 sujeitos portadores sintomáticos e assintomáticos de PAF-TTR, recrutada como as anteriores na consulta regular da Unidade Corino de Andrade, e um grupo controlo, formado por uma amostra de conveniência de 30 sujeitos da população em geral, não portadores de doença crónica e/ou hereditária conhecidas.

3. Instrumentos

Para a realização dos estudos incluídos neste trabalho, foram utilizados, para além do Questionário Sociodemográfico, os seguintes instrumentos:

3.1. Questionário de História da Doença Pessoal e Familiar

A presença de inúmeros factos existenciais ligados a situações de luto e perdas provocados pela doença tem sido reconhecida, empiricamente, principalmente em contexto clínico. Trabalhos de investigação anteriores não publicados davam também conta desse mesmo facto, o que constituía sem dúvida uma questão importante e que seria necessário investigar. Foi decidida a construção de um instrumento (questionário) que pudesse responder, tanto quanto possível a essas questões.

Este questionário foi construído especificamente para este trabalho. Em estudos prévios (não publicados) foram investigados temas biográficos e psicossociais relacionados com a doença, em portadores da Val30Met, a partir de uma entrevista semiestruturada. Esta foi posteriormente avaliada, por análise de conteúdo, e foram determinados os temas considerados relevantes na sua biografia pessoal e história familiar que queríamos determinar e avaliar. Estas constituíram a base das questões que foram incluídas neste questionário. Os temas fundamentais foram: 1) morte ou doença de progenitor; 2) idade do sujeito à morte ou doença do progenitor; 3) ter sido cuidador(a) do progenitor doente; 4) relação entre conhecimento da doença, contacto com a doença e o seu próprio diagnóstico; 5) impacto pessoal da doença; 6) mudanças de vida relacionadas com a doença; 7) mudanças de residência para outra localidade; e 8) mudanças psicológicas ou emocionais provocadas pela doença.

O questionário (ver anexos) incluiu também perguntas relativas à procura de diagnóstico genético e outras relacionadas com eventual história psiquiátrica.

3.2. BSI-53 - Brief Symptom Inventory-53

As dificuldades de estudar psicopatologia, de forma sistemática, em populações determinadas, são bem conhecidas e prendem-se principalmente com a escolha dos instrumentos de avaliação.

Os trabalhos de investigação inseridos nesta tese pretenderam fazer uma abordagem sistemática a essa problemática, não constituindo a única finalidade do trabalho, o que poderia acontecer se a opção tivesse passado por um instrumento mais específico de pesquisa psicopatológica.

O BSI foi a escolha possível. Não permitindo fazer diagnósticos psiquiátricos, o BSI avalia, no entanto, as dimensões fundamentais de psicopatologia. Tem sido utilizado em doentes com doença física, e os seus índices totais permitem, pela presença de sintomas

psicopatológicos, avaliar situações de *distress* emocional, que necessitam ser sempre levadas em conta mesmo na ausência de diagnósticos psiquiátricos. Este sofrimento psicológico ou mal estar emocional envolvido na vivência da doença física, nomeadamente nas doenças crónicas, poderá ter neste constructo, *distress,* uma explicitação importante e a ter em conta na organização de cuidados de saúde (L. R. Derogatis, 1993; Leonard R Derogatis & Wise, 1989).

O BSI tem a vantagem de estar validado para a população portuguesa, apresentando boas caraterísticas psicométricas (M. C. Canavarro, 2007). Esta autora definiu valores normativos para a população portuguesa para os índices globais do instrumento. Foram incluídas as restantes dimensões do inventário, na comparação entre grupos, nas correlações e nos modelos de regressão multivariada. O inventário apresentou também boas características psicométricas na população específica, aqui estudada.

Esta escala tem sido utilizada em trabalhos de investigação sobre psicopatologia em doenças físicas, de que referenciamos, necessariamente, apenas alguns (Dale et al., 2016; Forkmann et al., 2011; Margalho, Pereira, Ouakinin, & Canavarro, 2011; Menear et al., 2015; Merport, Bober, Grose, & Recklitis, 2012; Thomas, 2012).

3.3. EVA – Escala de Vinculação do Adulto

A escala de vinculação do adulto (EVA) usada nos estudos 4 e 6, é a única escala quantitativa traduzida e validada para a população portuguesa (M Cristina Canavarro, Dias, & Lima, 2006). É a tradução do *Adult Attachment Scale-R* (Collins & Read, 1990) e constituiu a nossa escolha, já que a alternativa, a Entrevista de Vinculação do Adulto, tradução da *Adult Attachment Interview* (George et al., 1996), imporia uma avaliação não quantitativa mas sim qualitativa, implicando uma dedicação de tempo e recursos de que não dispúnhamos.

A escala possui boas qualidades psicométricas que foram replicadas no estudo atual.

3.4. FACES – Family Adaptability and Choesion Evaluation Scales versão IV

Este questionário foi aplicado a portadores da mutação Val30Met, seus cônjuges e doentes com esclerose múltipla para responder aos objetivos 5 e 6.

A procura de um instrumento para avaliação do sistema e dinâmica familiares teve desde logo constrangimentos semelhantes à procura dos anteriores: era necessário um

instrumento com boas qualidades psicométricas, já suficientemente experimentado, validado ou pelo menos já utilizado e testado em populações portuguesas.

Num trabalho de investigação anteriormente realizado com doentes com PAF, e que constituiu também um trabalho de mestrado, utilizámos a versão anterior deste instrumento (FACES III). A versão atual (v. IV), parece trazer vantagens com classificações mais claras e coerentes na avaliação dos sistemas familiares (David Olson, 2011).

Numa revisão sistemática de instrumentos de autoavaliação de famílias, com base em propriedades psicométricas, modelos teóricos subjacentes e utilidade clínica, o FACES IV foi revisto em conjunto com outras sete escalas de avaliação familiar. O FACES IV foi uma das escalas consideradas como tendo qualidades requeridas para o seu uso (Hamilton & Carr, 2016).

A escala foi utilizada em Portugal, e num destes estudos foram avaliadas as suas propriedades psicométricas, sendo os resultados bastante positivos (J. C. Carvalho, Freitas, Leuschner, & Olson, 2014; Pereira & Teixeira, 2013).

Sendo a família, como unidade, o objeto do presente estudo e o seu funcionamento e avaliação, esta escala parecia a mais adequada a este caso.

Os dados obtidos pelo *FACES IV* foram pontuados de acordo com a folha de Excel disponibilizada pelo autor, que permite resultados para todas as dimensões avaliadas assim como os *circumplex ratio scores (*valores do *ratio* para a flexibilidade, para a coesão e o *ratio* total).

4. Avaliação ética e processo de consentimento informado

Todos os procedimentos incluídos nestes estudos foram aprovados pela Comissão de Ética do Centro Hospitalar do Porto. Estes procedimentos estão de acordo com a Declaração de Helsínquia e com a sua última emenda.

Todos os participantes deram o seu consentimento informado e assinaram um termo específico para o estudo, de acordo com o protocolo aprovado pela Comissão de Ética do Centro Hospitalar do Porto.

CAPÍTULO 3

RESULTADOS

Estudo Preliminar

O estudo preliminar identificou e caraterizou dimensões de vinculação do adulto e comparou-as com as de uma amostra da população geral, relacionando-as com as dimensões psicopatológicas do BSI, nomeadamente ansiedade, depressão e somatização.

ATTR amyloidosis

Familial Dynamics, Attachment and Psychopathology in Familial Amyloidotic Polyneuropathy Patients

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Studies on familial dynamics, attachment and psychopathology in Familial Amyloidotic Polyneuropathy (FAP) are few. In 31 FAP patients and a control group (n=30) were applied: socio-demographic and familial description questionnaire, Adult Attachment Scale (AAS) and Brief Symptoms Inventory (BSI). Most of patients were females, married, had one child, were retired and 35,5% had lost one of parents at childhood/adolescence. Patients mean age was 42,4y (control group 36,8y). Statistically significant differences were found between groups for AAS dimensions (Closeness and Dependence, p<0,001). Female patients presented higher Anxiety (p<0,001). Also were found statistically significant differences between groups for all BSI dimensions (p<0,05) (except for Paranoid Ideation). Female patients had higher values for Depression, Anxiety and Obsessive-Compulsive dimensions (p<0,05). These imply that FAP patients are a special group with particular familial characteristics, with difficulties in attachment that may be responsible for psychopathology patterns. Females represent the more problematic group.

INTRODUCTION

Studies on familial dynamics and attachment in Familial Amyloidotic Polyneuropathy (FAP) patients are few. There isn't much information about psychopathology in these patients.

For a long time, patients with FAP lived with a disease that had no treatment, had to face a chronic and catastrophic evolution that most of them knew very well, since they had experienced it in other members of their families (parents, siblings and even other members of their communities). FAP has a great impact on mental and relational patients life (psychosocial and familial)[1,2].

The hereditary characteristics with variable adulthood age of onset and the variable symptomatic expression provokes uncertainty and anxiety; chronic and devastating evolution full of repulsive aspects of the body may decrease self esteem, evoke feelings of rejection, loneliness and depression. These patients live with a disease that imposes a strong psychological burden to them and their families[3]. Liver transplantation and most recently a new specific medication (tafamidis) have brought some hope for these patients but also a new source of anxiety (to be or not to be included, whether for transplantation or for medication)[4].

It is known that chronic diseases cause an important impact in families. In the area of other genetic late onset diseases a few studies have made relevant how these families may be more problematic (cohesion, emotions expression) and attachment issues have been also addressed[5,6].

Studies on families with FAP, concerning the psychosocial impact of disease on family structure are relevant to develop therapeutic strategies that may fit these population problems.

With this study we wanted to know if families with FAP do organize in a different way of families with no such problems, and if their members have particular attachment patterns and psychopathology?

METHODOLOGY

This is a preliminary, transversal and quantitative study. The sample was composed by two groups, one with patients consecutive attending consultation in Familial Amyloidotic Unit, Centro Hospitalar do Porto (*n*=31), and the other, control group (*n=30*), with subjects without known genetic or chronic disease. All of participants were more than 21 and less than 66 years old.

The following instruments were used: Socio Demographic Questionnaire, Familial Description Questionnaire, Adult Attachment Scale (AAS) and Brief Symptom Inventory (BSI).

AAS has 18 items for evaluation of 3 dimensions: *Closeness* (comfort in making relationships), *Dependence* (feelings of depending on others) and *Anxiety* (concerns about being abandoned or rejected by others)[7]. BSI has 53 items that evaluate 9 psychopathological dimensions (*Somatization*, *Obsessive/Compulsive*, *Interpersonal Sensivity*, *Depression*, *Anxiety*, *Hostility*, *Phobic Anxiety*, *Paranoid Ideation* and *Psychoticism*) and 3 global indexes (*Global Severity Index*, *Positive Symptom Distress Index* and *Positive Symptom Total*)[8]: In this study, besides the nine dimensions, we only consider the Global Severity Index which helps to measure the overall psychological distress level.

For statistical analysis was used the Student t test for independent samples. When was not verified the assumption of normality, was used the Mann-Whitney test. All analysis were performed using the SPSS version 17.0 and was considered the significance level p=0,05.

RESULTS

Most patients were waiting for liver transplantation (64,5%); 25,8% were in advanced stage and 9,7% have been transplanted; 64,5% were female and 67,7% were married (50% in the control group). Mean age of patients was 42,4y (*SD*=10,0) and 36,8y (*SD*=11,7) in control group. Most of patients had 1 child (44,8%) or none (24,1%); in control group, 56,7% had no children and 16,7% had one child. Most of patients had less than 9 years of school level and most of control group had more than 12 years of school level. Most of patients belonged to the working class and had no professional qualifications. 61,3% are retired and 89,5% of these, because of FAP. Only 3,6% are retired in the control group.

Results from Familial Description Questionnaire: the sick parent was in 58,6% the mother and all sick parents were deceased; parents age of beginning of sickness was 39,8 yrs (*SD*=10,8 yrs, *Min*=28 yrs, *Max*= 61 yrs) and the mean age of patients at that time was 13,3 yrs (*SD*=9,5 yrs, *Min*=1 yr, *Max*=30 yrs). At date of decease, the mean age of *parents* was 51,7 yrs (*SD*=11,4 yrs, *Min*=32 yrs, *Max*=77 yrs) and the mean age of *patients* was 23,7 yrs (*SD*=10,5 yrs, *Min*=5 yrs , *Max*=46 yrs).

Most of patients (80%) referred they had no separations or significant life changes after sick parents death.

Results from AAS: were found statistically significant differences between the two groups for dimensions Closeness and Dependence (p<0,001). Considering only the FAP group, were verified that women presented a higher score in Anxiety (p<0,001) and that there were no differences regarding the marital status (p>0,05 in all dimensions) or loss of progenitor in childhood/adolescence (p>0,05 in all dimensions).

Results from BSI: were found statistically significant differences between the two groups for all BSI dimensions (p<0,05) (except for Paranoid Ideation). FAP group had a higher median score for all BSI dimensions and, considering the results of this group regarding the gender, were verified that women had higher values and presented statistically significant differences for Obsessive-Compulsive (p=0,031), Depression (p=0,033), Phobic Anxiety (p=0,044) and Paranoid Ideation (p=0,041) dimensions.

DISCUSSION AND CONCLUSIONS

Patients had higher scores in almost all psychopathologic indexes than control group, which could define FAP patients as a vulnerable group with higher risks for emotional/psychiatric breakdowns. Depression and anxiety were the most common problems in these patients. Patients had also more difficulties with adult attachment. This means that FAP patients may be more vulnerable to problems of depending on others and closeness. This may have as consequence difficulties in adult relationships and intimacy.

When we considered the variable gender, we found that women with FAP are at higher risk for several psychopathological problems namely depression and anxiety.

In patients there were a very high percentage of sick or deceased parents during childhood and/or adolescence. Although we empirically know that those events may provoke significant life changes, in this sample such did not occur. Also no changes were found whether in psychopathology or attachment issues, related to these variables which according to literature of other domains, could be expected.

The study limitations namely the sample size and the fact that only few of studied patients had significant life changes after sick parent's sickness or death could explain that such implications were not relevant.

Emotional and psychopathological problems are common and relevant, so these patients should have available psychosocial support in multidisciplinary teams.

This is a preliminary study and although these results may be limited they represent certainly the need to obtain more rigorous knowledge about psychopathology, emotional problems and familial issues in FAP patients.

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Estudo 1

O estudo 1 teve como finalidade o objetivo explicitado 1, isto é, descrever e caracterizar acontecimentos de vida, pessoais e familiares, percebidos como estando relacionados com a doença, ao longo da vida dos participantes com a “mutação” Val30Met na TTR, e discussão das suas possíveis implicações sociais.

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ORIGINAL ARTICLE

Life paths of patients with transthyretin-related familial amyloid polyneuropathy Val30Met: a descriptive study

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Abstract Transthyretin-related familial amyloid polyneuropathy Val30Met is a fatal progressive disease. It is a rare hereditary amyloidosis, manifesting as a sensorimotor neuropathy and autonomic dysfunction. It begins during adulthood and is a disabling disease, posing a great psychological burden to patients and their families. Our aim was to describe and characterize life events related to the disease and discuss its psychosocial implications. Social and demographic data and a questionnaire on history of family and personal disease, and biographic events, were applied to 209 subjects attending an outpatient specialized clinic. Descriptive and statistical analyses were performed. They were 84 men and 127 women belonging to three groups: pre-symptomatic carriers, patients, and subjects with no established diagnosis. Most subjects were married/lived with a partner and had children (mean of 4). Most (96.3%) had contact with the disease before having a diagnosis; the affected or at-risk parent was the mother in 53.8% and the father in 43.3%; 71.8% of these had deceased. At their parent's death, many subjects were aged under 10 (9.9%), 10–14 (15.5%), or 15–24 years (31.7%). Most were under age 14 (44.9%) at their parent's disease onset; 37.2% referred this brought life changes with psychological and familial impact; most had been parent's caregivers; 7.5% had not been raised by the parents. Some (8.4%) declined to know their genetic tests results for over 1 year. Parent's disease and death are very common early in these patient's lives. During childhood or youth, many subjects became caregivers, implying changes in family roles. This disease and its life implications pose a significant psychosocial burden since childhood. TTR-FAP patients and their relatives are highly vulnerable to emotional stress and psychopathology during their lifetime. Psychological and psychiatric support, implying a multidisciplinary group, must thus be available for all of them.

Keywords Transthyretin · TTR · Familial amyloid polyneuropathy · Amyloidosis · Psychosocial · Psychiatric · Life events

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Introduction

Transthyretin-related familial amyloid polyneuropathy Val30Met (TTR-FAP) is a progressive, life-threatening disease, which manifests as a mixed sensorimotor neuropathy and autonomic dysfunction (Coelho et al. 1994; Coutinho

et al. 1980). The disorder is due to a point mutation (Val30Met) in TTR, a transport protein for thyroid hormone and retinol that deposit as amyloid in endoneurial spaces and organs (Ando and Ueda 2012; Benson and Kincaid 2007; Merlini and Westermark 2004; Saraiva 1996). The mutant protein is mainly produced not only in the liver (95%) but also in the choroid plexus in the central nervous system (CNS) and the retina (Benson and Kincaid 2007; Sekijima et al. 2008).

It is a rare inherited autosomal dominant amyloidosis. TTR-FAP occurs worldwide, but has its most important clusters in Sweden, in Japan (Holmgren et al. 1994; Koike et al. 2002; Parman et al. 2016; Sousa et al. 1993), and in the north of Portugal (Sousa et al. 1995). More than 3700 patients have been registered at our central hospital, since Corino Andrade observed the first patient in 1939 (Andrade 1952). Age of onset of symptoms is highly variable and unpredictable among and even within families and the disease may have early or late onset (after fifties) (Conceição 2012; Koike et al. 2002; Koike et al. 2012; Sousa 1995, 2006). Onset occurs before age 40 years, and a mean age of 38 years was found in a Portuguese sample (Santos et al. 2016). In northern Portugal, where its prevalence is very high (90.3/100,000), mean age-at-onset is earlier (29 in men; 33.7 in women) (Coutinho et al. 1980; Hou et al. 2007; Sousa et al. 1990, 1995).

The disease has a variable clinical expression, the peripheral and autonomic neuropathy being one of the major problems, with sensory and motor, as well as gastrointestinal, bladder, and cardiac problems, until a cachectic bedridden stage (Adams et al. 2000; Conceição 2012). Amyloid deposits also occur in the eyes (vitreous opacities, iris irregularities, glaucoma), kidneys (microalbuminuria to end-stage renal failure), heart (conduction disturbances), and CNS (Beirao et al. 2011; Lobato and Rocha 2012; Maia et al. 2015). Symptoms provoke great incapacity and psychosocial burden, including sexual dysfunction, changes in body image, uncontrollable diarrhea, and loss of sphincter control. In advanced stages of disease, patients lose autonomy and become dependent for daily life activities (Jonsen et al. 1998) .

For a long time, there was no treatment for this disorder and patients died within a period of 11 years, on average, after appearance of the first symptoms (Coutinho et al. 1980). Since 1990, liver transplantation has been performed as a way to slow disease progression, by preventing liver production of mutant TTR (Adams 2013; Ericzon et al. 2015; Holmgren et al. 1991; Suhr et al. 1995). In recent years, tafamidis, a drug that decreases amyloid deposition by stabilizing TTR, became an additional possible treatment. Other drugs and forms of treatment are being studied or under clinical trials (Berk et al. 2013; Coelho et al. 2013; Ueda and Ando 2014). Current available treatments slow down the disease progression and modify its natural history (Adams 2013; Coelho et al. 2013).

The familial and hereditary characteristics of this disease, beyond its chronicity and devastating progression, pose a strong psychological impact upon the lives of these patients and their relatives (Lopes 2003). Patients have preserved fertile years (women more so, due to their slightly later onset and to sexual dysfunction in men as an early symptom), marry, and have children (Sousa 1995). Onset, more often in mid 20s to mid 30s, and its progression for over a decade, even when available treatments are delivered, impose a heavy presence of the disease in these families' lives. When it appears, it may change usual family patterns with economic, social and family losses as it is described for other chronic conditions (Breier et al. 1988). Thus, it is expected that during childhood, adolescence, and as young adults, members of these families may experience important life events related to the disease and its history in the family. Early parental loss and trauma have been studied as a cause of psychopathological distress early in life and later in adulthood (McLaughlin et al. 2012; Tyrka et al. 2008b). The impact of a chronic disease in one of the parents as a cause of family dysfunction and psychological problems in children has been reported (Bogosian et al. 2010; Steck et al. 2007). Vamos et al. (2007) assessed a group of adults who grew up in a household with a parent with Huntington's disease and concluded that adverse parenting were present in both parents, the HD positive and HD negative (Vamos et al. 2007). The aim of this study is to describe and characterize personal, social, and familial life events perceived as related to TTR-FAP along patients' lifetime and to discuss the psychosocial implications these may have.

Methods

Participants

The sample consisted of 209 adults (85 men and 124 women) with the Val30Met mutation. They were regularly followed at external consultation at the Corino de Andrade Unit of Centro Hospitalar do Porto: 109 participants had an established diagnosis of TTR-FAP in different evolution stages, 81 were proven asymptomatic carriers and 19 had no established diagnosis. This group either had symptoms but no amyloid deposits on biopsy or had amyloid on biopsy but no symptoms; although for this group there were no onset of symptoms, this group was also included because they suffer a psychosocial burden as diagnosed patients and asymptomatic carriers do. This was a non-probabilistic sequential convenience sample. All subjects aged 18 to 65 years were eligible to be included in the study. Participants were recruited between 2013 and 2015, at their routine consultation and agreed to answer the study questionnaires. A single investigator approached participants about taking part in the study and presented them the instruments. The institutional review board of Centro

Hospital do Porto approved the study, and written consent was obtained from all study participants.

Instruments

The study included two questionnaires: a social and demographical form and a questionnaire about the *Family and Personal History Disease*. Our research group developed this questionnaire specifically for this study. It was based on information provided by previous unpublished studies, where we had evaluated, by content analysis, results from a semi-structured interview addressing biographical facts perceived by patients with TTR-FAP, as relevant to their lives, and that they related to family and personal history of the disease. In this questionnaire, we considered the following as relevant: (1) the disease or death of parents; (2) the subject's age at parent's death or at parent's disease onset; (3) having cared for a sick parent; (4) the relation between knowledge and contact with disease and their own diagnosis, and how this happened; (5) life impact of the disease; (6) perceived life changes imposed by the disease, as having been moved to another caregiver family or other non-related persons; (7) having changed address; and (8) perceived psychological or emotional changes. In this *Family and Personal History*, (9) questions about seeking predictive test and time until disclosure of results were other relevant issues registered. (10) Moreover, the questionnaire had also questions addressing psychiatric issues, like attending or having attended psychiatric or clinical psychology appointments, previous or current use of any psychiatric drugs, and known psychiatric diagnoses the subject may have had. The questionnaire had multiple choice and *yes* or *no* questions. In three questions, participants were invited to elaborate on particular issues using free text. For these responses, a content analysis was conducted; however, the findings are not presented in this paper.

Statistical analysis

Quantitative variables were summarized as mean and standard deviation (SD). Categorical variables were reported as percentages. Proportions between subgroups were compared with chi-squared test. All statistical analyses were done with the SPSS software package, version 23.0 (Chicago, IL).

Results

Two hundred and nine subjects (59% female) completed the study protocol; 81 were asymptomatic carriers for TTR-FAP (mean age: 33.9±9.8 years); 109 were diagnosed as patients (mean age: 38.0±8.1 years); 19 had no established diagnosis, because they did not fulfill yet the necessary clinical criteria: they had some clinical symptoms, but no amyloid in biopsies, or biopsies with amyloid deposits, but no clinical findings (mean age, 40.9 ± 4.0 years). In the total sample, 15.8% were retired and 4.8% on sick leave. Most (59.3%) finished their basic education (9th year of schooling), but only 17.2% completed high school (12 years) and 21.5% had a university degree; four participants (1.9%) were illiterate. Considering only affected patients (n = 108), most (52.8%) were still actively working, 25.9% were retired, 13.0% were unemployed, and 8.3% were on a sick leave. In the total sample, most subjects were married or lived with a partner (68.4%) and 61.5% had children (mean children, 1.34±0.8, with a maximum of 4). Almost all of subjects (96.3%) had some contact with the disease before having their diagnosis, mainly through an affected parent (36.1%) or other family members (52.9%). The sick parent was the mother in 52.2% of the subjects, and the father in 45.0%. About 71.1% of sick parents were deceased, and, among those who were alive, most (76.0%) had symptoms of the disease.

Most subjects (57%) were under 24 years of age when their parents died due to TTR-FAP: 9.9% were 10 years of age or younger; 15.5% were between age 10 and 14 years; and 31.6% were aged 15 to 24 years; the remaining were older than 25 years (43%) when their affected parent died. The majority of the subjects were under 24 years of age at their parent's onset: 30.5% were under age 10 years, and the remaining were between age 10 and 14 years old (13.2%), between 15 and 24 (27.0%), and 18.4% were older than 25 years old age (Table 1).

When asked about whether and how the parent's disease had brought changes into their lives, 37.6% of the subjects answered yes, namely in terms of change in residence and familial and psychological modifications, which were felt as adverse. No significant differences were found when this was related to the sick progenitor (in 42.5%, the mother was the sick progenitor vs. 37.3%) (p = 0.455).

Fear of the future, changes in how life was seen, giving up school to help family needs, feelings of growing up faster, living with the parent's disease and thinking about that possibility for their own future, giving up playing, and feeling not having a normal childhood were some of the expressed perceptions of changes that the disease had brought.

Most subjects (53.9%) had been their parent's caregivers; of these, 54.7% were women and 52.5% were men (p = 0.778). A person other than their parents had cared for about 7.6% during their childhood and youth; the mother or the mother and another relative had cared for 36.3%, and the father or the father and another family member had cared for 2.4%.

When asked about pre-symptomatic testing and time of result disclosure, most subjects (79.5%) received their test results after completing genetic tests. Other at-risk subjects (8.4%) were genetically tested but declined to know their available results for more than 1 year (one of them only until

Table 1 Descriptive characteristics of the study sample

	N (%)
Study sample (n = 209)	
Asymptomatic carriers	81 (38.8)
TTR-FAP patients	109 (52.2)
No established diagnosis	19 (9.1)
Gender (female)	124 (59.3)
Age (> 35 years)	102 (48.8)
Marital status	
Married or living with a partner	143 (68.4)
Single	47 (22.5)
Divorced/separated	15 (17.2)
Widowed	4 (1.9)
With children	99 (47.4)
Professional situation	
Active	14 (67.0)
Retired	33 (15.8)
Sick leave	10 (4.8)
Unemployed	26 (12.4)
Age at parents' death	
≤ 14 years old	34 (24.5)
15 to 24 years old	44 (31.7)
≥ 25 years old	61 (43.9)
Age at parents' disease onset	
≤ 14 years old	76 (36.4)
15 to 24 years old	47 (22.5)
≥ 25 years old	32 (15.3)

8 years later). Only 1.4% of all subjects had known their genetic status when they were already symptomatic. When asked, 36.7% answered that the genetic test results had an impact on their lives. Changing plans about having children or concerns about them were among the most frequently reported; psychological impact and difficulties in coping with a *carrier* result were also reported, as well as changes in sentimental relationships. Some referred to inability to have a serious relationship and three respondents had divorced after the genetic test results.

Around 26.5% of all participants reported psychological or psychiatric problems in the past and 18.2% in the year before taking part in this study. There were no sex differences (p = 0.108), but affected patients were more likely to have had such problems than asymptomatic carriers were (p = 0.017); 21.2% were taking medication, namely anti-depressive drugs and/or tranquilizers. The most frequent diagnosis established by a psychiatrist or family doctor was depression and anxiety, and three patients were diagnosed as having an obsessive-compulsive disorder.

Discussion

A great number of subjects in our sample had a lifetime charged with distressful life events related to the presence of TTR-FAP in the family. Disease and death of a parent were frequent occurrences before young adulthood. Other consequences in that period of life, and possibly connected to it, included family disruption such as moving home, and being cared only by one parent or by another member of the family; a significant number of subjects reported psychological and emotional distress. Most of these subjects knew the disease well and its consequences from their sick parents and other relatives and had substantial previous contact with the disease. Moreover, they also knew its hereditary characteristics. We believe this knowledge and perception may possibly act as a permanent threat, in a subjective way, whether in the past, present, or future. Their parent's illness had already begun at a time when most participants were still under age 14 years; thus, most of them lived with a sick parent during their childhood or adolescence. Considering the severe incapacity imposed by the disease, this implies a great burden upon these families, with these children often having an actual parental loss because of death or at least, a parent that is not available due to disability. Adverse parenthood has been reported in families with other disabling, chronic diseases, namely Huntington disease, which shares some genetic and clinical characteristics with TTR-FAP (as late onset, physical incapacitation and having no cure) (Cerel et al. 2006). Additionally, more than half of the participants in our study reported having been a caregiver for their sick parent's. In our sample, although more daughters had this task, it was not significantly different from sons. Caring for these patients is a very demanding task and it seemed a very difficult challenge to face for a child, adolescent, or young adult; this reflects the perception that offspring, even as young children, have about the importance of their role as caring for their affected parent. Reports of feelings of "growing up fast" may also relate to the needs offspring had been obliged to fulfill, including becoming caregivers for a sick parent and/or giving up school to work and help financially at home.

More than half had lost their sick parent before the age of 24 years. Bereavement in childhood because of parental death is pointed as the most important stressor a child can live, and, although some say that its psychiatric effects are not yet fully understood, others have concluded that children that suffer depression in the context of parental depression and other stressors in the family are at the greatest risk for psychopathological distress and depression (Cerel et al. 2006; Tennant 1988). Beyond the effects in childhood, adolescence has been also the object of similar studies (Zajac and Kobak 2009). The effect of early parental loss and of parental depression has been related to future psychopathology during adulthood (Benjet et al. 2010; Hovens et al. 2010; Luecken 2000;

Stikkelbroek et al. 2012). Putative biological mechanisms for this have also been suggested: neuroendocrine effects of experiencing an early loss associate to decreased salivary cortisol responses to awakening and are believed to reflect an altered hypothalamic-pituitary-adrenal axis, which could explain the increased risk for stress-related disorders later in life (Meinlschmidt and Heim 2005; Nicolson 2004; Tyrka et al. 2008a). Depression and anxiety were referred by a significant number of participants. Also, a significant number of subjects reported psychological or psychiatric problems in the past, and approximately 20% were taking psychopharmacologic medication at the time, mostly antidepressants (with SSRI and mirtazapine being the most used). We may discuss if this increased vulnerability to psychological distress and psychopathology are related to early life events, namely parental loss or parental illness, to the continuous threat posed by a carrier status, or because of living with a chronic disabling disease and its consequences. In our study, we could not determine if the disease and death of a mother was more devastating than that of a father. A greater risk to psychopathological consequences in adulthood has been assigned to an early mother's loss, compared to that of a father (Agid et al. 1999; Brown et al. 1977). In this study, a small number of subjects reported that they had been cared by the father or by the father and another family member, when the sick parent was the mother, while a much more significant number of subjects stated they had been cared by the mother or the mother and another relative, when the sick parent was the father. This may mean that it is possible that when the affected parent is the mother, children may experience more life changes and eventually be more distressed. Nevertheless, the reduced number of offspring in our sample raised solely by a father or with the help of another relative made comparisons difficult. This hypothesis should be further investigated.

Anxiety and depression related to genetic testing have been reported in subjects at risk for hereditary, late-onset neurological disease, namely in Huntington and Machado-Joseph diseases (Gonzalez et al. 2004, 2012; Tibben 2007; Timman et al. 2004; van der Meer et al. 2015). Similar results were found in TTR-FAP at-risk subjects who looked for and did genetic testing (Ledo et al. 2016; Lêdo et al. 2016; Paneque et al. 2009; Rolim et al. 2006). In the present study, emotional distress around genetic testing was also referred. For some subjects, this created a major problem, and several of them have delayed receiving their pre-symptomatic test results for more than 1 year. For a small number of subjects, disclosure of their genetic status seemed very difficult challenge to face. That way, psychological denial of their genetic risk was maintained until the beginning of symptoms. In the case of these subjects, all admitted knowing they had the disease. In Portugal, specific legislation requires that persons at-risk seeking pre-symptomatic testing for these late-onset diseases receive pre- and post-test genetic counseling and psychosocial evaluation and follow-up, according to a national protocol for late-onset genetic diseases (Sequeiros et al. 2006); however, some chose not to be tested and a number of subjects gave up the counseling protocol before disclosure of results. Avoidance and denial may act in those subjects as the only coping mechanisms. These findings corroborate the need for psychosocial support during the process of genetic testing, included in established protocols. We also think that for several reasons, some of study respondent's may have not be included in the counseling protocol and did not have enough psychosocial support which possibly explains the difficulty to disclose results.

Concerns about procreation and future disease in offspring were some of the most important consequences of getting a pre-symptomatic or an affected diagnosis. Although prenatal diagnosis and preimplantation genetic diagnosis (PGD) are available, these procedures are not without constraints, particularly psychological and emotional ones (Carvalho et al. 2001; Dreesen et al. 2014; Land and Evers 2003; Sequeiros et al. 1998). One respondent claimed she made seven unsuccessful attempts at PGD. Some responded that they had decided not to have children, but we could not know if these subjects had already made any frustrated attempt to have children, if PGD posed some constraints to them or if other reasons were present.

In conclusion, TTR-FAP patients, persons at the pre-symptomatic stage and those still at genetic risk for the disease experience several stressful life events throughout their lives, which may begin as soon as their childhood. Loss and illness of a parent and psychological and effective changes in family life are among the most important, early in life. Occurrence of later life events is also relevant, though we cannot predict how significant they may be for future psychopathological problems. The decision about up taking pre-symptomatic testing once they reach adult life and seeking reproductive options are, nevertheless, other sources of psychosocial distress.

TTR-FAP patients and their relatives are, thus, a vulnerable group to emotional stress and psychopathology during their lifetime. Psychological and psychiatric support must be available for these patients and their families, including young children. This implies a multidisciplinary team, where genetic counselors, clinical psychologists, and psychiatrists should participate and should be organized for the best possible care of these patients and families.

Systematic follow-up for pre-symptomatic carriers and patients in reference centers is highly recommended. Studies on psychopathology in children and during adulthood, including family structure and functioning, still lacking, should be undertaken to clarify its possible relation with the potential life events in TTR-FAP families.

Compliance with ethical standards The institutional review board of Centro Hospital do Porto approved the study, and written consent was obtained from all study participants.

Conflict of interest Alice Lopes has received honoraria from Pfizer for presentations at courses of TTR-related FAP for physicians.

Alexandra Sousa has no conflicts to disclosure.

Isabel Fonseca has no conflicts to disclosure.

Margarida Branco has no conflicts to disclosure.

Carla Rodrigues has no conflicts to disclosure.

Jorge Sequeiros has received honoraria from Pfizer for presentations on genetic counseling of TTR-related FAP, at international meetings (ARiA) and courses for physicians, as well as for the preparation of leaflets and webminars on genetic counseling of TTR-related FAP.

Teresa Coelho received support from Pfizer, IONIS Pharmaceuticals, and Alnylam pharmaceuticals to attend scientific meetings and integrates the speakers' bureau of Pfizer and received honoraria.

Paula Freitas has no conflicts to disclosure.

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Estudo 2

O estudo 2 teve como finalidade o objetivo 2, isto é avaliar dimensões psicopatológicas e sintomas psicopatológicos em portadores sintomáticos e assintomáticos da “mutação” e compará-los com a população em geral.

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Research Article

Psychopathological Dimensions in Portuguese Subjects with Transthyretin Familial Amyloid Polyneuropathy

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What Is It about?

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a fatal, chronic, progressive disease. It is a rare hereditary amyloidosis, which manifests as a sensorimotor neuropathy and autonomic dysfunction. It begins during adulthood. There are very few studies about psychopathology in these patients and asymptomatic carriers. The present study evaluated psychopathological dimensions in this particular population. It concluded that many FAP patients and carriers had more psychopathological symptoms than the general population, when Brief Symptom Inventory (BSI) was applied. It also concluded that patients have higher risk for most of psychopathological dimensions. In addition, women are more vulnerable, and with time, patients have more psychological distress.

Keywords

Transthyretin familial amyloid polyneuropathy · Familial amyloid polyneuropathy · Psychosocial issues · Psychopathology · Psychiatric issues

Abstract

Background: Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a fatal, chronic, progressive disease. It is a rare hereditary amyloidosis, which manifests as a sensorimotor neuropathy and autonomic dysfunction. It begins during adulthood. ***Aims and Methods:*** Our aim is to evaluate psychopathological dimensions in a population attending a consultation center for TTR-FAP. Two hundred and nine subjects (symptomatic and asymptomatic carriers), 84 men and 127, women participated in the study. Most subjects were married (67.1%) and most of them were still working; 33% were retired from work or on a sick leave. A sociodemograph-

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ic questionnaire and The Brief Symptom Inventory (BSI) were applied. Statistical analysis was performed (descriptive analysis, Mann-Whitney, Wilcoxon, and Spearman tests). ***Results:*** The Global Symptom Index (GSI) was significantly higher in patients (p = 0.001). Considering GSI, 32.7% of total subjects were above the median for general population. When subgroups were evaluated, 25.6% of symptomatic carriers, 26.3% of subjects without established diagnosis, and 39.1% of patients were above median. GSI was significantly higher in patients (p = 0.001). Some BSI dimensions were also significantly higher in the patient group (somatization, depression, anxiety, and psychoticism) when compared with carriers. Women scored higher than men. Sick women scored higher for all dimensions except somatization. Asymptomatic carriers scored statistically higher for phobic anxiety (p = 0.01), interpersonal sensitivity, anxiety, and depression. In patients, most dimensions and GSI (rho = 0.33, p = 0.002) had positive correlations with years of disease. ***Conclusions:*** TTR-FAP patients and carriers are a very vulnerable group for psychological distress and psychopathological problems. Women and patients are at higher risk.

Introduction

Chronic diseases have important psychosocial consequences that demand significant psychological adaptive processes. They represent permanent threats and challenges for these patients, which must be addressed by an emotional balance that may be missing on several occasions. Chronic diseases impose diagnosis doubts, incapacities, loss of autonomy and quality of life, uncertainty about the future along with social and familial changes.

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare and fatal inherited amyloidosis of adult onset. Age at onset is variable and unpredictable, and the disease may have early or late onset (after 50s) [1–3]. It is a chronic, progressive disorder caused by generalized deposition of mutated TTR [4–8]. The disease is transmitted in an autosomal dominant way, with a penetrance that approaches 100% in the areas of higher prevalence. Although TTR Val30Met mutation occurs worldwide, the largest focus is located in the north of Portugal [9–11]. Andrade [12] observed the first patient in 1939, and since then more than 3,700 patients have been registered at our center in Hospital Santo António, Porto.

TTR-FAP is a devastating disease leading to autonomy loss and causing death in around 11 years, when no treatment is implemented [13]. The clinical picture is dominated by a mixed sensory, motor, and autonomic neuropathy; severe nephrological, cardiac, ophthalmological, vesical, gastrointestinal, sexual, and central nervous system symptoms are related to systemic amyloid deposition [14–18].

For a long time, patients with TTR-FAP lived with a disease that had no treatment and had to face a chronic and catastrophic clinical evolution. The characteristics of heredity with variable age at onset in adulthood and variable symptomatic expression, and the chronic and devastating evolution pose a psychological burden on these patients and their families. The disease has a great impact on the mental and relational life of these patients [19].

Since the 1990s, liver transplantation is a possibility for these patients precluding the synthesis of abnormal protein. In recent years, tafamidis, a drug that prevents mutated protein deposition, became another available treatment. Both treatments slow down the disease progression and increase patient survival [20–24].

The following studies concerning psychosocial issues in TTR-FAP, included patients before and after liver transplantation, and in the genetic testing context. The need for psychological coping and psychiatric issues have been considered in liver transplantation [25, 26]. After transplantation, when comparing different etiologies of hepatic diseases, mental quality

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of life improved for several hepatic diseases, but worsened for FAP patients. Some other studies found no differences in psychiatric diagnosis between patients with TTR-FAP and those with alcohol liver disease, while they were on the waiting list [27, 28]. A few phenomenological studies described the experience of Swedish TTR-FAP patients submitted to liver transplantation. According to these, the experience had a positive as well as a negative connotation: the threat of a fatal disease was gone, but in spite of liver transplantation, patients remained symptomatic and disabled needing continuous psychological and social support [29, 30].

Distress and psychopathological issues were studied in genetic screening, before and after presymptomatic testing. No negative outcomes were found in short-term psychosocial impact of genetic testing. Moreover, genetic screening seemed to improve the psychological well-being of persons at risk, and pretest levels of anxiety and depression were good predictors of that improvement. Apart from that, family dynamics seemed important in the pretest phase and for test uptake, lessening the psychological impact of testing results [31–33]. Medium- and long-term psychosocial impact of presymptomatic testing showed how depression and anxiety varied in subjects: depression occurred only when subjects had previously manifested the first symptoms of their neurological disease and the proximity to the age at symptom onset might be a trigger for anxiety [34, 35].

As a chronic, progressive and disabling disease, TTR-FAP imposes a psychological burden on patients and mutation carriers, and we may expect psychopathological problems in these subjects. Depression and anxiety have been reported as the most relevant symptoms reported in a liaison psychiatry consultation in a study that included 30 TTR-FAP patients [36]. Thus, the aim of present study is to evaluate psychopathological dimensions and symptoms in a consecutive sample of TTR-FAP patients and carriers, and compare them with the general population.

Methods

Participants

The study sample included 209 adults (85 men and 124 women) with the Val30Met mutation. They were followed in consultation at the Unidade Corino de Andrade of Centro Hospitalar do Porto. One hundred and nine participants had an established diagnosis of TTR-FAP in different evolution stages, 81 were proven asymptomatic carriers, and 19 had no established diagnosis since they had symptoms without a positive amyloid biopsy or a positive biopsy without symptoms. All subjects aged 18–65 years were eligible to be included in the study. Participants were recruited at their routine consultation and agreed to answer the study questionnaires. All procedures performed in this study were approved and in accordance with the ethical statements of the Centro Hospitalar do Porto Ethical Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All study participants gave written consent.

Instruments

Two questionnaires were applied to all subjects: Brief Symptom Inventory (BSI-53) and a social demographic questionnaire that also included three questions addressing psychiatric issues, like attending or having attended psychiatric or clinical psychology appointments, previous or current use of any psychiatric drugs, and known psychiatric diagnoses the subject may have had.

The BSI-53 is a screening tool used for detecting psychopathological symptoms as indicators of emotional distress. It consists of a self-rated questionnaire with 53 items that are

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answered on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (extremely). The BSI-53 has nine subscales, which assess nine domains of psychopathology: Somatization, Obsessive-compulsive, Interpersonal sensitivity, Depression, Anxiety, Anger-hostility, Phobic anxiety, Paranoid ideation, and Psychoticism. Three global indices of distress were computed: Global Symptom Index (GSI), Positive Symptom Index (PSI), and Positive Symptom Total (PST). GSI represents a combined assessment of intensity of distress and the number of symptoms; PSI gives a media of intensity for all symptoms and PST represents the number of signalized symptoms.

Derogatis developed the BSI in 1982 [37, 38]. The validated Portuguese version of BSI-53 was used in this study [39]. The mean values of global indices obtained for the Portuguese population were 0.83 (standard deviation, SD = 0.48) for GSI, 26.99 (SD = 11.72) for PSI, and 1.56 (SD = 0.38) for PST.

Subjects filled out the forms in the presence of the same investigator, who assisted in the process of filling, solving doubts that respondents might have.

Statistical Analysis

Preliminary tests for normal distribution, outliers, and missing data were conducted. Descriptive analysis included frequency and percentage, mean and SD, or median and interquartile range. Cronbach's α statistics measured internal consistency of the BSI-53 scale as a whole and each of its nine subscales. Guttman split-half statistic further evaluated the BSI-53 internal reliability. Data were nonnormally distributed for all BSI dimensions. Several attempts were done to normalize data without success; thus, nonparametric tests were used in most analyses. Correlations with and among the BSI scales were computed using Spearman correlation (rho). For continuous variables, groups were compared with the Mann-Whitney *t* test.

Multivariable logistic regression was performed to determine whether selected variables were associated with higher scores of GSI, PST, and PSI as dependent binary variables (higher or lower than the means levels achieved for Portuguese population). The independent variables included in the models were tested to evaluate their effect on the occurrence of psychological symptoms evaluated by GSI, PST, and PSI. Multivariate linear regression analysis was applied to investigate possible related variables with each BSI dimension as the dependent variable. Statistical significance was defined as $p < 0.05$, and all analyses were done with the statistical package SPSS version 23.0.

Results

There were 209 subjects (86 men; 123 women) included in this analysis: 81 carriers (nonsymptomatic), 109 patients, and 19 with no established diagnosis. This is a group of participants, positive for TTR-FAP, regularly followed at our center for evaluation; they have not yet a defined status of having initiated the disease. They may have symptoms that sometimes may be confounding and have not positive biopsies for amyloid. They were included in present research because we were not making clinical research about the beginning of disease, but in the psychosocial aspects of having a genetic disease of late onset. Besides these particular clinical aspects, they share all other investigated issues with patients and carriers without disease.

The mean age at participation was 37 (SD = 9.7) years, with 50% of the sample being 35 years old or younger. The mean age was lower for carriers (34 years, SD = 9.8) and higher for subjects with no established diagnosis (41 years, SD = 14), with a mean age of 38 years (SD = 8.1) for FAP patients. In FAP patients, the median time of disease evolution was 4 years (range: 1–28 years).

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Table 1. Internal consistency of the nine BSI-53 dimensions and the total score

	Cronbach's α
Somatization (BSI.S)	0.89
Obsession-compulsion (BSI.OC)	0.80
Interpersonal sensitivity (BSI.IS)	0.82
Depression (BSI.D)	0.88
Anxiety (BSI.A)	0.83
Hostility (BSI.H)	0.79
Phobic anxiety (BSI.PA)	0.79
Paranoid ideation (BSI.PI)	0.80
Psychoticism (BSI.P)	0.68

Most of the subjects were married or lived with a partner (68.4%), and most of them were still working (67%); 15.8% were retired from work or on a sick leave (4.8%). The majority of participants (59.3%) completed the basic education (9th year of schooling), 17.2% completed the high school, and 21.5% had a college degree. Four participants (1.9%) were illiterate.

Scale Reliability: Internal Consistency

The total BSI-53 score demonstrated good reliability (Cronbach's α = 0.97; Guttman split half reliability = 0.87). The internal consistency of the nine subscale scores was examined by using Cronbach's α. The lower Cronbach's α was 0.68 for psychoticism, and the remaining coefficients ranged from 0.78 to 0.9 (Table 1).

BSI-53 Global Indices (GSI, PST, and PSI)

The mean GSI score was 0.76 (SD = 0.63), median = 0.58. Considering the mean levels of Portuguese general population [39], 35.4% were above the mean levels for general population (mean = 0.83, SD = 0.48). Considering the subgroups, 28.2% of nonsymptomatic carriers, 29.4% of subjects without established diagnosis, and 41.7% of patients were above mean levels of GSI. The mean PST levels for the global sample were 22.9 (SD = 14.1), median = 21.0, and 38.4% were above mean levels for general population (mean = 27.0, SD = 11.7). Considering the subgroups, 29.5% of nonsymptomatic carriers, 41.2% of subjects without established diagnosis and 44.7% of patients were above mean levels of PSI. The mean PSI scores for the total sample were 1.59 (SD = 0.56), median = 1.50, and 44.4% were above mean levels for general population. Considering the subgroups of subjects, 39.7% of nonsymptomatic carriers, 52.9% of subjects without established diagnosis, and 46.6% of patients were above mean levels of general population.

BSI-53 Comparisons

Subgroups of Subjects (Nonsymptomatic Carriers, Symptomatic Carriers, and Subjects with No Established Diagnosis)

Descriptive statistics for BSI dimensions and global indices for nonsymptomatic and symptomatic carriers are presented in Table 2. Median levels of all dimensions of BSI were higher in the group of patients when compared with that of the carriers, but only somatization, depression, anxiety, and psychoticism showed a statistically significant difference. The median levels of GSI and PST were significantly higher in patients than in carriers, but not PSI. The sample of subjects with no established diagnosis was also compared with nonsymptomatic carriers. No significant differences were found in the median score of any of the BSI dimensions or global indexes, except for PSI with lower median levels for subjects with no established diagnosis (0.66 [0.26–1.0] vs. 1.46 [1.14–1.78], p = 0.02). We did not find significant differences between subjects with no established diagnosis and FAP patients.

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Table 2. Descriptive statistics for BSI dimensions and global indices for nonsymptomatic and symptomatic carriers

	Nonsymptomatic median (IQ)	FAP patients median (IQ)	*p*
Somatization	0.29 (0.00–0.71)	0.86 (0.29–1.43)	**<0.001****
Obsession-compulsion	0.83 (0.46–1.21)	1.00 (0.50–1.50)	0.368
Interpersonal sensitivity	0.50 (0.00–1.25)	0.50 (0.00–1.25)	0.899
Depression	0.33 (0.17–1.00)	0.67 (0.17–1.67)	**0.006***
Anxiety	0.50 (0.17–0.83)	0.83 (0.17–1.33)	**0.044***
Hostility	0.50 (0.20–1.20)	0.60 (0.40–1.40)	0.137
Phobic anxiety	0.00 (0.00–0.40)	0.20 (0.00–0.60)	0.409
Paranoid ideation	0.80 (0.35–1.60)	0.80 (0.40–1.60)	0.539
Psychoticism	0.20 (0.00–0.60)	0.40 (0.00–0.80)	**0.019***
GSI	0.44 (0.21–0.93)	0.68 (0.38–1.25)	**0.014***
PST	16 (10–31)	24 (15–37)	**0.010***
PSI	1.46 (1.14–1.78)	1.53 (1.21–1.95)	0.108

GSI, Global Symptom Index; PST, Positive Symptoms Total; PSI, Positive Symptoms Index.

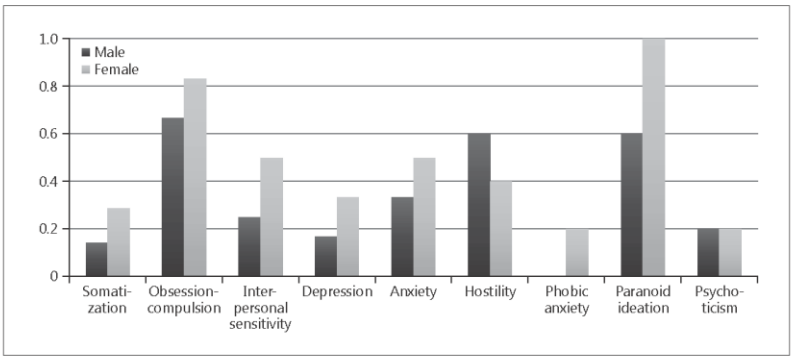

Fig. 1. Differences in BSI dimensions, considering gender, in symptomatic carriers only.

Gender

When we considered differences between gender, women who were asymptomatic carriers had statistically significantly more interpersonal sensitivity ($p = 0.042$) and more phobic anxiety ($p = 0.017$). There were no significant differences in GSI, PST, or PSI. In the group of patients, almost all dimensions were scored significantly higher for women, with the exception of somatization, which was almost significant ($p = 0.052$). GSI, PST, and PSI were also significantly higher in women (Fig. 1).

Marital Status

The median scores of the nine BSI subscales and global indices were compared between subjects married or living with a partner versus others (separated/divorced/single/widowed), but no significant differences were found either in patients or in asymptomatic carriers.

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Table 3. Independent predictors of a GSI, PST, and PSI higher than the mean levels achieved for the Portuguese population in TTR-FAP patients

	OR adjusted	*p* value	95% CI
Independent predictors of GSI >0.83			
Gender (female vs. male)	3.55	0.004	1.51–8.35
Disease evolution time (per each year of increase)	1.07	0.026	1.01–1.14
Independent predictors of PST >26.99			
Gender (female vs. male)	3.79	0.002	1.60–8.98
Disease evolution time (per each year of increase)	1.09	0.007	1.03–1.17
Independent predictors of PSI >1.56			
Gender (female vs. male)	3.07	0.008	1.34–7.05
Disease evolution time (per each year of increase)	1.07	0.029	1.01–1.14

Results given by logistic regression (forward Wald test), considering the Global Symptom Index (GSI), Positive Symptom Total (PST), and Positive Symptom Index (PSI) categorized according the mean levels achieved for the Portuguese population (higher or lower) as the dependent variable. The subgroups of 19 subjects with no established diagnosis and 81 asymptomatic carriers were excluded in these analyses. The variables disease evolution time (years), age (continuous), gender, professional occupation (nonactive vs. active), marital status (married/living with a partner vs. others), and having children (yes vs. no) were included in the models. OR, odds ratio; 95% CI, 95% confidence interval; TTR-FAP, transthyretin familial amyloid polyneuropathy.

Professional Occupation

When we analyzed differences in BSI scores and global indices considering the professional occupation (still working vs. others, that is retired, unemployed, or on a sick leave), no significant differences were found in the group of asymptomatic carriers. In the group of patients, the subjects professionally active had significant lower BSI scores in somatization ($p = 0.002$), obsessive-compulsive ($p = 0.014$), depression ($p = 0.040$), and phobic anxiety ($p = 0.01$). The GSI and PSI global indices were also significantly lower in patients with an active professional situation versus others ($p = 0.038$ and $p = 0.002$, respectively).

Correlations

In the group of patients, all BSI dimensions and GSI (rho = 0.31, $p = 0.001$), PST (rho = 0.29, $p = 0.003$), and PSI (rho = 0.24, $p = 0.016$) had positive correlations with years of disease, except for interpersonal sensitivity.

Independent Predictors of GSI, PST, and PSI in TTR-FAP Patients

This analysis only included symptomatic patients. The variables disease evolution time (years), age (continuous), gender (female vs. male), professional occupation (nonactive vs. active), marital status (married/living with a partner vs. others), and having children (yes vs. no) were included in the models.

The independent predictors of GSI >0.83 were female gender (vs. male: OR = 3.55, $p = 0.004$) and longer disease evolution time (per each year of increase: OR = 1.074, $p = 0.026$). The independent predictors of PST >26.99 were female gender (vs. male: OR = 3.79, $p = 0.002$) and longer disease evolution time (per each year of increase: OR = 1.095, $p = 0.007$). Regarding PSI, the independent predictors of a PSI >1.56 were also female gender (vs. male: OR = 3.07, $p = 0.008$) and longer disease evolution time (per each year of increase: OR = 1.073, $p = 0.029$) (Table 3).

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Table 4. Independent predictors of each BSI dimension in TTR-FAP patients

	Regression coefficient adjusted	*p* value	95% CI
Independent predictors of BSI Anxiety			
Gender (female vs. male)	0.579	<0.001	0.309–0.849
Disease evolution time (per each year of increase)	0.026	0.009	0.007–0.046
Marital status (married/living with a partner vs. others)	0.316	0.040	0.014–0.618
Independent predictors of BSI Somatization			
Gender (female vs. male)	0.378	0.017	0.068–0.688
Being professionally nonactive (yes vs. no)	0.358	0.032	0.032–0.683
Marital status (married/living with... vs. others)	0.334	0.017	0.014–0.618
Disease evolution time (per each year of increase)	0.043	0.001	0.019–0.067
Independent predictors of BSI Obsession-compulsion			
Gender (female vs. male)	0.615	<0.001	0.336–0.894
Being professionally nonactive (yes vs. no)	0.451	0.004	0.147–0.755
Marital status (married/living with... vs. others)	0.334	0.039	0.018–0.650
Disease evolution time (per each year of increase)	0.022	0.043	0.001–0.044
Independent predictors of BSI Paranoid ideation			
Gender (female vs. male)	0.414	0.008	0.110–0.717
Disease evolution time (per each year of increase)	0.024	0.033	0.002–0.046
Independent predictors of BSI Hostility			
Gender (female vs. male)	0.028	0.006	0.008–0.049
Disease evolution time (per each year of increase)	0.358	0.011	0.082–0.634
Independent predictors of BSI Depression			
Gender (female vs. male)	0.466	0.003	0.157–0.774
Disease evolution time (per each year of increase)	0.033	0.004	0.011–0.056
Independent predictors of PSI Psychoticism			
Gender (female vs. male)	0.289	0.009	0.073–0.505
Disease evolution time (per each year of increase)	0.018	0.030	0.002–0.033
Independent predictors of BSI Interpersonal sensitivity			
Gender (female vs. male)	0.536	<0.001	0.258–0.813
Independent predictors of BSI Phobic anxiety			
Gender (female vs. male)	0.462	<0.001	0.242–0.683
Being professionally non-active (yes vs. no)	0.381	0.001	0.154–0.607
Marital status (married/living with... vs. others)	0.254	0.049	0.001–0.507

Independent Predictors of Each BSI Dimension in TTR-FAP Patients

The independent predictors of higher BSI Somatization and BSI Obsession-compulsion were: disease evolution time (more years); female gender; having children; and being professionally nonactive. The results are summarized below and displayed in Table 4.

The independent predictor of higher BSI Interpersonal sensitivity was only the female gender. The independent predictors of higher BSI Depression, BSI Hostility, BSI Paranoid ideation and BSI Psychoticism were female gender and higher disease evolution time (years). The independent predictors of higher BSI Anxiety were female gender, marital status "married/living with a partner," and greater disease evolution time (years). The independent predictors of higher BSI Phobic anxiety were female gender, marital status "married/living with a partner," and being professionally nonactive.

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Psychiatric and Psychological Problems

Around 26.5% of subjects reported psychological or psychiatric problems in the past and 18.2% in the year before responding to the protocol; 21.2% were taking medication, namely antidepressive drugs and/or tranquilizers. The most frequent diagnosis established by a psychiatrist or family doctor was depression and anxiety, and 3 patients were diagnosed as having obsessive-compulsive disorder.

Discussion

Chronic medical illness and chronic neurological diseases have been associated with depression, anxiety, and emotional distress [40–46]. Literature has shown that psychopathological comorbidities may worsen the prognosis and quality of life in patients with medical illnesses [47]. In these patients, an increase in mortality was found [48–50].

The criteria for psychiatric diagnosis may be very difficult when a patient has a comorbid medical disorder. In serious chronic medical conditions, medical and psychiatric symptoms may overlap and diagnostics may be complicated. Nevertheless, in these conditions, we must pay attention to emotional pain and emotional distress. In 1989, Derogatis and Wise raised the issue that in chronic medical illness, states of psychological distress, although not enough for a psychiatric diagnosis, are associated with high levels of discomfort and reduced quality of life.

The BSI questionnaire has been widely used not only in patients with psychiatric disorders but also patients with chronic medical illnesses to evaluate psychological and psychiatric comorbid symptoms and psychological distress [51–56].

According to its authors, BSI "possess a broad range of sensitivity to symptomatic manifestations, ranging from mild loss of well-being with few if any clinical implications through morbid distress states to symptom levels characteristic of formal psychiatric disorders. These instruments not only may help in operationalizing diagnostic status but are sensitive to a comprehensive range of psychological distress states" [57, p. 81].

In the present study, BSI-53 showed good reliability with internal consistency coefficient results that were similar to those reported by Canavarro's group who performed a study to validate this questionnaire in a Portuguese community sample.

To our knowledge, beyond transplantation and genetic testing, no literature exists addressing psychopathology in TTR-FAP subjects. In liver transplantation, more mental problems and psychological constraints were reported in TTR-FAP patients when compared with subjects with other diagnosis [27, 28, 30]. In genetic testing, anxiety and depression may exist on several occasions during the procedure: when subjects are waiting for results, after disclosure, and in the years after testing when subjects become symptomatic [31–35].

The results of the present study showed that percentages ranging between 29 and 52% of patients and carriers were above the mean levels for the general population in GSI, PST, and PSI dimensions of BSI. The symptomatic and asymptomatic groups demonstrated in a considerable number of subjects more psychopathological symptoms. These results point to the existence of high levels of psychosocial distress in this specific population. When these two groups were compared, it was noticed that the group of patients had higher levels for psychopathological symptoms. The median levels of global severity symptoms, as well as some of BSI dimensions (somatization, depression, anxiety and psychoticism) were significantly higher in patients than in carriers.

Our findings concerning symptomatic subjects are in agreement with the literature, when other chronic medical conditions are considered. Katon et al. [40] showed that depression was 2–3 times more frequent in chronic medical diseases. The psycho-oncology

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literature has shown that more than 30% of cancer patients meet the criteria for a mental condition diagnosis [58–60], and in chronic autoimmune diseases, psychiatric conditions and psychological distress are important associated problems [46, 47, 61–63]. Many chronic medical diseases are also associated with higher levels of mental problems [49, 64].

In this study, higher levels of psychopathological symptoms were also found in the asymptomatic group compared to the general population. Although these subjects do not have to face, yet, the disease and its consequences, they live with uncertainty about its onset, and most of them live or have lived with one or more sick relatives. This could concur with higher psychological distress among this group. In Huntington's disease, a late-onset neurological disorder that shares the characteristics of heritability and incurability with TTR-FAP, similar results were found. More cases of major depressive disorder and obsessive compulsive disorder were found in both presymptomatic and symptomatic mutation carriers than in the general population; psychiatric disorders were more prevalent in mutation carriers than in noncarriers [65, 66].

When gender was considered, sick women scored significantly higher on global BSI indices, and all other dimensions, except somatization. Asymptomatic women had significantly higher scores in interpersonal sensitivity and phobic anxiety. These values demonstrated that women are more at risk for psychopathological symptoms than men, and this was more evident when they were already sick. These results were supported by multivariable analysis, after adjusting for other social demographic variables. These findings are in accord with the epidemiology for mental health diseases that show a higher vulnerability, namely for anxiety and depression, in females [67–70].

All BSI dimensions and global indices positively correlated with years of disease. Similar findings were found in a study with Huntington disease where disease stage predicted anxiety and depression; however, sex did not [71]. Multivariable logistic regression analyses identified the independent predictors for BSI global indices higher than the mean levels found in general population. Being a woman and years of disease predicted higher levels in all three BSI global indices.

When subjects were asked about a history of psychological problems, depression and anxiety were the most referred diagnoses. These results are similar to those found in other chronic diseases where depression and anxiety are the most prevalent psychological/psychiatric problems.

A chronic physical illness must be considered more than a sum of signs and physical symptoms. Dekkers [72] pointed out to the fact that these patients have to face not only the diagnosis crisis but a series of crisis throughout the course of their illnesses. Adjustments must continuously be made as the illness progresses. Chronic illness is not static and imposes a permanent need of restructuring one's life [73, 74].

Conclusions

Results of the present study point to important vulnerabilities to psychological distress and psychiatric disease of asymptomatic and symptomatic carriers of TTR-FAP with the mutation Met30Val.

Becoming sick, years of disease, and female gender seem to play a major role in psychological associated symptoms in subjects with TTR-FAP.

Depression and anxiety were psychopathological dimensions observed in sick subjects, and they were the most frequently made diagnoses.

In TTR-FAP amyloidosis, like in other progressive chronic illness, patients must live with the uncertainty of how and when symptoms will begin, need to cope with permanent changes

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in functioning, body image, permanent threats to self-esteem and disruption of social roles as well as plans for future [75, 76].

In TTR-FAP patients and at-risk subjects, several factors are implicated in psychological distress and psychiatric disorders, and these certainly are multiple and complex. Some of them like being already sick, disease stage, and sex may be recognized, which may act as major stressors and be associated with psychological distress. Many subjects with this mutation experience, from very early in their lives, changes in family functioning, disease in close relatives, and parental loss, among others, as disease consequences. However, early-life events were not considered in this current analysis.

As in other chronic illnesses, psychological and psychiatric support is very important to these patients and at-risk subjects. Therefore, multidisciplinary teams that assist these populations should include professionals of these areas.

Study Limitations

The study sample included only Portuguese subjects with TTR-FAP V30M. Because of that, its results cannot be extrapolated to other amyloidosis cases whether with the same variant but in different countries or cultures or with genetic variants with different clinical problems and different outcomes.

The approach to psychopathological issues provided by BSI may have limitations as psychiatric diagnosis cannot be made. Further research is needed to address more accurate psychiatric diagnosis in these subjects.

Statement of Ethics

All procedures performed in this study were approved and in accordance with the ethical standards of the Centro Hospitalar do Porto Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

A. Lopes has received honoraria from Pfizer for presentations at courses of TTR-related FAP. T. Coelho has received support from Pfizer, Ionis Pharmaceuticals, and Alnylan Pharmaceuticals to attend scientific meetings, integrates the speaker's bureau of Pfizer, and received honoraria. J. Sequeiros received honoraria from Pfizer for presentations on genetic counselling of TTR-related FAP and courses, as well as preparation of leaflets and webminars on genetic counselling.

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Estudo 3

O estudo 3 teve como finalidade o objetivo 3, verificando como e se os acontecimentos de vida relacionados com a doença, assim percebidos pelos sujeitos com a mutação Val30Met, se associavam às dimensões psicopatológicas encontradas nesta população.

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ORIGINAL ARTICLE

Psychopathological dimensions in subjects with hereditary ATTR V30M amyloidosis and their relation with life events due to the disease

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ABSTRACT

Background: Chronic physical illness has been associated with emotional distress. Chronic diseases may change usual family patterns with economic, social and family losses. Hereditary ATTR V30M amyloidosis is a rare, fatal inherited systemic amyloidosis, with chronic evolution and beginning in adulthood.

Aims and methods: To evaluate psychopathological dimensions and how they correlated with disease-related life events, 209 symptomatic and asymptomatic carriers, participated in the study. Sociodemographic and *Family and Personal History Disease* questionnaires and brief symptom inventory (BSI) were applied.

Results: BSI indices, global severity index (GSI), positive symptom index (PSI) and positive symptom total (PST) scored higher than general population. Independent predictors for GSI >0.83 were female sex (OR = 3.46, $p = .005$) and being symptomatic carriers (OR = 3.03, $p = .039$). Independent predictors of a PST >26.99 were female sex (OR = 3.74, $p = .012$) symptomatic carrier (OR = 5.32, $p = .025$), age between 15 and 24 years at affected parent's death (OR = 5.26, $p = .04$). Independent predictors of a PSI >1.56 were being asymptomatic carrier (OR = 6.3, $p = .036$); to have children (OR = 3.19, $p = .043$) and have ≤14 years at parent's disease onset (OR = 6.39, $p = .05$).

Conclusions: Results point to an important vulnerability of this population for psychological distress and psychiatric disease. Early life events related to disease, being sick and sex are associated with psychopathological distress.

Abbreviations: BSI-53: Brief Symptom Inventory; CI: Confidence Interval; GSI: Global Severity Index; h-ATTR V30M amyloidosis: Hereditary ATTR amyloidosis Val30Met; IQ: Inter Quartile; IQR: median and interquartile range; LT: liver transplantation; OR: Odds Ratio; PSI: Positive Symptom Index; PST: Positive Symptom Total; rho: Spearman test; SD: standard deviation; TTR: transthyretin

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Introduction

Chronic medical illness and, in particular, chronic neurological diseases have been associated with depression, anxiety and emotional distress. Numerous literature has shown that psychopathological comorbilities may worsen prognosis and quality of life in these patients, and are associated with a raise of morbidity and mortality [1–10].

Chronic diseases impose their heavy presence in families' lives and may change family patterns, due to economic, social and family losses [11]. During childhood, adolescence and as young adults, members of these families may experience important life events related to the disease impact in family life. Early parental loss and other traumatic events have been studied as a cause of psychopathological distress early in life and later in adulthood [12,13]. The impact of chronic disease in a parent as a cause of family dysfunction and psychological problems in children has been studied [14,15]. Razaz [16] evaluated the children of patients with multiple sclerosis and concluded that parenting stress, parental depression and parental chronic disease constituted life stressors for their mental health. Vamos et al. assessed a group of adults who grew up in a household with a parent with Huntington's disease and concluded for adverse parenting by both affected and unaffected parents [17].

Hereditary (h-) ATTR V30M amyloidosis is a rare and fatal systemic, inherited amyloidosis. It is caused by mutation of transthyretin that deposit as extracellular amyloid fibrils [18–20]. It is transmitted in an autosomal dominant way, with a lifetime penetrance approaching 100% in the areas of higher prevalence [21,22]. Although the h-ATTR V30M amyloidosis occurs worldwide, its largest foci are in Sweden, Japan and the north of Portugal [23–26]. Age of onset is variable and unpredictable, and although the disease may have early or late onset it usually occurs after the

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second decade of life [21,24,27–29]. A mean age of around 38 years was found in a Portuguese sample [30]. The clinical picture is dominated by a severe sensory-motor and autonomic neuropathy. It also includes serious nephrological, cardiac, ophthalmological, vesical, gastrointestinal symptoms and sexual dysfunctions, causing disability, dependence and death after a mean duration of 11 years if no treatment is undertaken [31–34]. During the last two decades, liver transplant became an available treatment, considering the predominantly hepatic synthesis of the abnormal protein [31,35]. Tafamidis, a drug that prevents amyloid deposition, became also accessible recently. These treatments slow down disease progression and improve patients' survival [36–39]. For a long time, patients and their families lived with a disease that had no treatment and had to face a chronic, catastrophic evolution. Most patients grew knowing well this situation, since they had seen it in their family (parents, siblings or other relatives) and other members in their community.

Hereditary characteristics, onset in adulthood, variable clinical expression and chronic and devastating evolution, pose a heavy psychological burden to these patients and their families and have a great impact on their mental and relational life [40].

There are few studies concerning psychosocial issues in h-ATTR V30M amyloidosis patients. Psychological and psychiatric issues have been studied in patients who had liver transplantation (LT) and in the context of pre-symptomatic genetic testing. When compared to other disease groups, these patients had more depression and anxiety while waiting for transplant [41,42]. Short-term psychosocial impact of pre-symptomatic testing showed no negative outcomes, and although some distress was present before and after genetic testing, it seemed to improve the psychological well being of persons at risk; pre-test levels of anxiety and depression were good predictors of that improvement [43,44]. These results could be related to the end of uncertainty and also to the fact that more resilient and emotionally stable subjects looked for genetic testing [45]. Studies about medium and long-term impact of pre-symptomatic testing showed that proximity to the age of onset can trigger anxiety; depression occurred only when subjects had already experienced the first symptoms [46–48]. Depression and anxiety were also reported as the most relevant symptoms reported in a liaison-psychiatry consultation in a study including 30 patients [49].

Asymptomatic and symptomatic carriers of h-ATTR V30M amyloidosis have, in general, preserved fertility. Affected women have children during a longer period of time than men, due to a slightly later onset [21]. Disease onset, more often in mid 20s to 30s, and its progression for over a decade, even if available treatments are provided, imply that families have to deal with one sick parent, and live with all the psychological, familial and social implications of the disease.

The aim of this study is to evaluate if and how personal, social and familial life events related to the disease, along the lifetime of h-ATTR V30M amyloidosis asymptomatic and symptomatic carriers, associate with psychopathological dimensions in this population.

Materials and methods

Participants

The sample was composed by 209 adults (85 men and 124 women) with the Val30Met mutation: 109 had an established diagnosis of h-ATTR V30M amyloidosis in different evolution stages, 81 were asymptomatic carriers and 19 had no confirmed disease onset. In this group, it was not certain whether the disease had already started because either they had symptoms but no amyloid deposits on biopsy or had amyloid on biopsy but no symptoms. They were included in this study because it had a psychosocial scope and no other clinical aspects. This was a non-probabilistic sequential convenience sample. All subjects aged 18–65 years were eligible to be included in the study. Participants were recruited at their routine external consultation, between 2013 and 2015, and agreed to answer the study questionnaires. A single investigator approached participants about taking part in the study and presented them the instruments.

All procedures were approved and in accordance with the ethical standards of the institutional ethical commitee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all study participants.

Instruments

Participants completed three questionnaires, conducted by a single investigator: the brief symptom inventory (BSI-53), a social demographic survey and a questionnaire about the *Family and Personal History Disease*.

The BSI-53 first developed in 1982 [50], is a screening tool for psychopathological symptoms, as indicators of psychological distress. It is a self-rated questionnaire with 53 items, answered on a 5-point Likert-type scale, ranging 0 (not at all) to 4 (extremely). It has nine subscales, assessing nine domains of psychopathological dimensions: somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation and psychoticism. Three global indices of distress were computed: global severity index (GSI), positive symptom index (PSI) and positive symptom total (PST). GSI represents a combined assessment of intensity of distress and the number of symptoms, and is a sensitive indicator of overall psychological distress; PSI provides a media of intensity for all symptoms; and PST represents the number of signalled symptoms. The Portuguese version of BSI-53 validated for Portuguese population (1999, 2007) was used [51].

Family and Personal History Disease Questionnaire was elaborated by our research group, based on a previously unpublished study, where we had evaluated by content analysis, a semi-structured interview addressing biographical facts (a) perceived by patients with h-TTR amyloidosis V30M as relevant to their lives, (b) which they related to

family and (c) personal history of the disease. In this questionnaire, we considered as relevant: (1) disease onset or death of a parent; (2) subject's age at a parent's death or at parent's disease onset; (3) having cared for a sick parent; (4) relation between knowledge and personal contact with the disease and their own diagnosis; (5) impact of the disease on their lives (life changes perceived as imposed by the disease as having been moved to another caregiver family or other non-related persons or having changed address; and (6) perceived psychological or emotional changes. In this *Family and Personal History*, (7) questions about seeking predictive test and time until disclosure of results were other registered issues. (8) The questionnaire addressed psychiatric history issues, like attending or having attended psychiatric or clinical psychology appointments, previous or current use of any psychiatric drugs and known psychiatric diagnoses. These questions had multiple choice and *yes* or *no* answers.

Statistical analysis

Preliminary analysis of outliers and missing data was done and Kolmogorov–Smirnov testing was applied to assess normality of distribution for continuous variables. The descriptive analysis included frequency and percentage, mean and standard deviation (SD) or median and interquartile range (IQR). Cronbach's alpha statistics measured internal consistency of the BSI-53 scale, as a whole and of each of its nine subscales. Guttman split-half statistic further evaluated the BSI-53 internal reliability. Data were non-normally distributed for all BSI dimensions; several attempts to normalize data had no success, thus non-parametric tests were used in most analyses. Correlations with and among the BSI scales were computed using the Spearman test (rho). Continuous variables were compared with the Mann–Whitney t-test. A multivariable logistic regression was performed, to determine whether selected variables were associated with higher scores of GSI, PST and PSI as dependent binary variables (higher or lower than the mean levels achieved in the Portuguese population). Independent variables were tested to evaluate their effect on occurrence of psychological symptoms evaluated by GSI, PST and PSI. Multivariate linear regression analysis was applied to investigate variables possibly related to each of BSI dimensions, as the dependent variable. Statistical significance was defined as $p < .05$ and all analyses were done with the statistical package SPSS Statistics for Macintosh version 23.0 (IBM SPSS Statistics, Armonk, NY).

Results

Descriptive characteristics of the study sample are shown in Table 1. Mean age at participation was 37 (SD = 9.7) years, with 50% being 35 years or younger. Mean age was lower for asymptomatic carriers (34 years, SD = 9.8) and higher for subjects with no established diagnosis (41 years, SD = 14), with a mean age of 38 years (SD = 8.1) for amyloidosis patients. In h-ATTR V30M amyloidosis, the median time of disease duration was 4 years (range: 1–28 years).

Table 1. Descriptive characteristics of total sample.

	N (%)
Asymptomatic carriers	81 (38.8)
Patients	109 (52.2)
No established diagnosis	19 (9.1)
Sex	
Female	124 (59.3)
Male	86 (40.7)
Age	
>35 years	102 (48.8)
Marital status	
Married or with partner	143 (68.4)
Single	47 (22.5)
Divorced/separated	15 (17.2)
Widowed	4 (1.9)
Professional situation	
Active	140 (67.0)
Retired	33 (15.8)
Sick leave	10 (4.8)
Unemployed	26 (12.4)
Schooling Level	
4 years	26 (12.4)
5–9 years	98 (47.0)
High school (12 years of schooling)	45 (21.5)
University degree	45 (21.5)
Illiterate	4 (1.9)

Scale reliability: Internal consistency

The total BSI-53 score showed good reliability (Cronbach's α, 0.97; Guttman split-half reliability, 0.87). The internal consistency of the nine subscale scores was examined. The lower Cronbach's alpha was 0.68 for psychoticism and the remaining coefficients ranged from 0.78 to 0.9.

BSI-53 global indices (GSI, PST and PSI)

Mean GSI score was 0.76 (SD = 0.63, median = 0.58). Considering the mean levels for the Portuguese population [51], 35.4% are above it (mean = 0.83, SD = 0.48); 28.2% asymptomatic carriers, 29.4% subjects with no established diagnosis and 41.7% of patients were above population mean levels. Mean PST was 22.9 (SD = 14.1, median = 21.0); 38.4% were above the Portuguese population (mean = 27.0, SD = 11.7); 29.5% asymptomatic carriers, 41.2% subjects with no established diagnosis and 44.7% of patients were above the population mean. Mean PSI was 1.59 (SD = 0.56, median = 1.50), and 44.4% were above population mean levels; 39.7% asymptomatic carriers, 52.9% subjects with no established diagnosis and 46.6% of patients were above mean levels for the general population.

BSI-53 comparison and correlation

Subgroups of subjects (asymptomatic carriers, ATTR-FAP patients and subjects with no established diagnosis)

Comparison between median levels of BSI dimensions and global indices between asymptomatic carriers and patients are presented in Table 2. No significant differences were found in the median score of any of the BSI dimensions or global indices, when we compared subjects with no established diagnosis and asymptomatic carriers, except for PSI that is lower in subjects with no established diagnosis (0.66 [0.26–1.0] vs. 1.46 [1.14–1.78], $p = .02$).

Sex

Women who were asymptomatic carriers had more interpersonal sensitivity ($p = .042$) and more phobic anxiety ($p = .017$); anxiety and depression also approached significance (respectively, $p = .098$ and $p = .080$). In patients, all dimensions scored significantly higher for women, except for somatization, which had approached significance ($p = .052$). GSI, PST and PSI were also significantly higher in women (respectively, $p = .001$, $p = .001$ and $p = .006$).

Table 2. Descriptive statistics for BSI dimensions and global indices for patients and asymptomatic carriers for h-ATTR V30M amyloidosis.

	Asymptomatic carriers Median [IQ]	Patients Median [IQ]	*p* Value
Somatization	0.29 [0.00–0.71]	0.86 [0.29–1.43]	<.001**
Obsession–compulsion	0.83 [0.46–1.21]	1.00 [0.50–1.50]	.368
Interpersonal sensitivity	0.50 [0.00–1.25]	0.50 [0.00–1.25]	.899
Depression	0.33 [0.17–1.00]	0.67 [0.17–1.67]	.006*
Anxiety	0.50 [0.17–0.83]	0.83 [0.17–1.33]	.044*
Hostility	0.50 [0.20–1.20]	0.60 [0.40–1.40]	.137
Phobic anxiety	0.00 [0.00–0.40]	0.20 [0.00–0.60]	.409
Paranoid ideation	0.80 [0.35–1.60]	0.80 [0.40–1.60]	.539
Psychoticism	0.20 [0.00–0.60]	0.40 [0.00–0.80]	.019*
GSI	0.44 [0.21–0.93]	0.68 [0.38–1.25]	.014*
PST	16 [10–31]	24 [15–37]	.010*
PSI	1.46 [1.14–1.78]	1.53 [1.21–1.95]	.108

*$p < .05$; **$p < .001$.

Disease duration

In the group of patients, except for interpersonal sensitivity, all dimensions BSI dimensions and GSI (rho = 0.31, $p = .001$), PST (rho = 0.29, $p = .003$) and PSI (rho = 0.24, $p = .016$) were positively correlated with years of disease evolution.

Family and personal history disease questionnaire

Main results from Family and Personal History Disease Questionnaire are shown in Table 3. About how the parent's disease had brought changes into their lives, 37.6% answered *yes*, namely in terms of moving residence, or family and psychological modifications felt as adverse. No significant differences were found regarding sex of the affected parent (the mother in 42.5%, the father in 37.3%, $p = .455$). From the parents' caregivers, 54.7% were women and 52.5% were men ($p = .778$).

Most subjects (79.5%) received their presymptomatic test results after completing genetic counselling; 8.4% of the subjects declined to know their available results for more than 1 year and 1.4% of the total sample had known their genetic

Table 3. Family and personal history disease questionnaire.

	Total sample ($N = 209$) *n* (%)	Asymptomatic carriers ($N = 81$) *n* (%)	Patients ($N = 109$) *n* (%)	No established diagnosis ($N = 19$) *n* (%)
Contact with disease before own diagnosis				
Yes	155 (74.2)	37 (45.7)	104 (95.4)	14 (73.7)
Affected parent	55 (26.2)	10 (27.0)	43 (41.3)	2 (14.3)
Another relative	100 (47.8)	27 (73.0)	61 (58.7)	12 (85.7)
No	54 (25.8)	44 (54.3)	5 (4.6)	5 (26.3)
Affected parent				
Mother	113 (54.1)	39 (48.1)	65 (59.6)	9 (47.4)
Father	91 (43.5)	39 (48.1)	43 (39.4)	9 (47.4)
Unknown	4 (1.9)	2 (2.5)	1 (0.9)	1 (5.3)
Both	1 (0.5)	1 (1.2)	–	–
Affected parent situation				
Alive	58 (28.2)	41 (51.2)	14 (13.0)	3 (16.7)
Deceased	148 (71.8)	39 (48.8)	94 (87.0)	15 (83.3)
If alive, affected parent is symptomatic				
Yes	32 (55.2)	20 (48.8)	10 (71.4)	2 (66.7)
No	26 (44.8)	21 (51.2)	4 (28.6)	1 (33.3)
Age at affected parent disease onset				
<10 years	53 (26.0)	13 (16.7)	36 (33.3)	4 (22.2)
10–14 years	25 (12.3)	11 (14.1)	14 (13.0)	0 (0.0)
15–24 years	47 (23.0)	13 (16.7)	29 (26.9)	5 (27.8)
≥25 years	30 (14.7)	15 (19.2)	12 (11.1)	3 (16.7)
Unknown	19 (9.3)	15 (19.2)	1 (0.9)	3 (16.7)
Missing	30 (14.7)	11 (14.1)	16 (14.8)	3 (16.7)
Age at affected parent death				
<10 years	14 (9.5)	5 (12.8)	8 (8.5)	1 (6.7)
10–14 years	22 (14.9)	4 (10.3)	16 (17.0)	2 (13.3)
15–24 years	45 (30.4)	12 (30.8)	30 (31.9)	3 (20.0)
≥25 years	61 (41.2)	13 (33.3)	40 (42.6)	8 (53.3)
Missing	6 (4.1)	5 (12.8)	–	1 (6.7)
Affected parent caregiver				
Yes	89 (43.6)	22 (28.2)	58 (53.7)	9 (50.0)
No	78 (38.2)	29 (37.2)	44 (40.7)	5 (27.8)
Missing	37 (18.1)	27 (34.6)	6 (5.6)	4 (22.2)
Who care the participant during childhood and youth				
Mother	48 (23.0)	13 (16.0)	32 (29.4)	3 (5.8)
Father	3 (1.4)	1 (1.2)	1 (0.9)	1 (5.3)
Mother and father	77 (36.8)	36 (44.4)	36 (33.0)	5 (26.3)
Mother, father and others	26 (12.4)	11 (13.6)	10 (9.2)	5 (26.3)
Mother and others	25 (12.0)	6 (7.4)	17 (15.6)	2 (10.5)
Father and others	3 (1.4)	1 (1.2)	2 (1.8)	0 (0.0)
Others	27 (12.9)	13 (16.0)	11 (10.1)	3 (15.8)

status when they were symptomatic. Test results had impact on the lives of 36.7%.

Considering the total sample, 26.5% reported psychological or psychiatric problems in their past and 18.2% in the year before answering the questionnaire; 21.2% were taking anti-depressants or tranquilizers. The most frequent diagnoses (established by a psychiatrist or family doctor) were depression and/or anxiety, and three patients had been diagnosed as having an obsessive–compulsive disorder. Affected patients had more such problems than asymptomatic carriers did ($p = .017$).

Family and personal history disease questionnaire and BSI

Age at affected parent's disease onset ($n = 155$): median values of BSI global indices and dimensions scores were compared among the groups (≤14; 15–24; ≥25 years). Sub-scale median values for hostility were significantly different between the three age groups ($p = .016$), being higher (0.8) for those aged 14 and under at parent's onset disease. Similar differences were also found when considering only symptomatic patients ($p = .027$), but not within the group of asymptomatic carriers.

Age at affected parent's death ($n = 139$): 44% were older than 25 years; the remaining were 15–24 years (32%) or aged 14 or under (25%). In the global sample, no significant differences were found in BSI levels between the three age groups; the same happened when only FAP patients or only asymptomatic carriers were considered.

Participants (37.6%) that stated their parents' disease had brought changes into their lives had higher levels of hostility (0.9) when compared to those reporting no changes ($p = .034$).

Independent predictors of GSI, PST and PSI

Multivariable logistic regression analyses were done to identify the independent predictors of a GSI, PST and PSI higher than the mean levels achieved for Portuguese population (Table 4).

Perceived life changes imposed by the disease (yes vs. no), professional occupation (non-active vs. active) and marital status (married/living with a partner vs. others) were also included in the models but were not statistically significant.

Impact of affected mother vs. affected father

BSI dimensions and global indices were compared between subjects considering the sick parent (father or mother). No significant differences were found in BSI dimensions and global indices, except for the global index PST, which was significantly higher for subjects with father as the sick parent (1.53 [1.26–1.98] vs. 1.41 [1.14–1.84], $p = .036$). Stratifying this analysis according to the subjects' age group at the time of parent's disease onset no significant differences were found in BSI dimensions and global indices. However, subjects over 25 years at parent's disease onset whose sick parent has been the father showed higher significant median values of all BSI dimensions and global indices (Table 5). Considering the subject's age group when the sick parent died the median values of somatization, interpersonal sensitivity (almost significant), phobic anxiety, paranoid ideation and PST were significantly higher in subjects who were under 14 years old when the mother died comparatively to the subjects who were at the same age but the sick parent who has died was the father (Table 5).

Independent predictors of each BSI dimension

Finally, a multivariable linear regression was done to identify the independent predictors of each BSI dimension. The variables age of subjects at the time of parent's disease onset and age at the time of parent's death were included in the models as dummy variables (≤14 year vs. all others; and within 15–24 year vs. all others). The results are summarized in Table 6.

Table 4. Independent predictors in h-ATTR V30M amyloidosis patients or asymptomatic carriers of a GSI, PST and PSI higher than the mean levels found in the Portuguese population.

	OR adjusted*	*p* Value	95% CI
Independent predictors of GSI >0.83			
Sex (female vs. male)	3.10	.019	1.20–8.00
Study group (patients vs. asymptomatic carriers)	6.53	.021	1.32–32.3
Independent predictors of PST >26.99	–	–	–
Sex (female vs. male)	3.91	.010	1.39–10.9
Study group (patients vs. asymptomatic carriers)	5.52	.022	1.28–23.8
Age at parent's death (15–24 year vs. ≥25 year)	4.98	.005	1.61–15.4
Independent predictors of PSI >1.56	–	–	–
Age (per 1 year increase)	1.08	.045	1.00–1.18
Having children (yes vs. no)	3.10	.048	1.01–9.55
Study group (patients vs. asymptomatic carriers)	6.00	.040	1.09–33.1
Age at parent's disease onset (≤14 year vs. 15–24 year)	6.36	.005	1.75–23.1

Results are given by logistic regression (forward Wald test), considering the GSI, PST and PSI scores categorized according to mean levels in the Portuguese population (higher or lower) as the dependent variable.
The subgroup of 19 subjects with no established diagnosis was excluded in these analyses. The variables age (continuous), gender, affected or asymptomatic carrier parent (father or mother), age of subjects at parent's disease onset (≤14 year, 15–24 year, ≥25 year), age at parent's death (≤14 year, 15–24 year, ≥25 year), perceived life changes imposed by the disease (yes vs. no), professional occupation (non-active vs. active), having children (yes vs. no) and marital status (married/living with a partner vs. others) were included in the models.
*$p < .05$.

Table 5. Comparison between BSI dimensions and total indices between subjects ≤14 years at parent's disease onset and subjects ≥25 years old at parent's disease onset, considering sex of affected parent.

	Affected parent death			Affected parent disease onset		
	Subjects ≤14 years			Subjects ≥25 years		
	Father	Mother	*p* Value	Father	Mother	*p* Value
Somatization						
Median	0.29	1.07	.015*	1.00	0.57	.044*
IQ	[0.00–0.93]	[0.50–1.46]		[0.43–1.57]	[0.14–0.86]	
Obsession–compulsion						
Median	0.83	0.83	.297	1.67	0.50	<.001*
IQ	[0.33–1.08]	[0.50–1.67]		[1.17–2.17]	[0.17–0.83]	
Interpersonal sensitivity						
Median	0.25	0.75	.051	0.50	0.25	.015*
IQ	[0.00–0.75]	[0.25–1.63]		[0.00–1.75]	[0.00–0.75]	
Depression						
Median	0.33	0.75	.115	1.67	0.33	.010*
IQ	[0.17–1.00]	[0.33–2.04]		[0.33–1.83]	[0.17–0.67]	
Anxiety						
Median	0.50	0.83	.250	1.33	0.33	.012*
IQ	[0.17–1.08]	[0.17–1.96]		[0.83–1.50]	[0.00–0.83]	
Hostility						
Median	0.40	0.90	.152	1.40	0.40	.027*
IQ	[0.20–0.80]	[0.35–1.80]		[0.60–2.00]	[0.20–0.60]	
Phobic anxiety						
Median	0.00	0.50	.015*	0.40	0.00	.036*
IQ	[0.00–0.30]	[0.15–0.75]		[0.00–1.20]	[0.00–0.40]	
Paranoid ideation						
Median	0.60	1.40	.026*	1.80	0.60	.006*
IQ	[0.20–1.10]	[0.60–2.10]		[1.20–2.00]	[0.00–1.00]	
Psychoticism						
Median	0.20	0.60	.450	0.60	0.00	.014*
IQ	[0.00–0.80]	[0.00–0.90]		[0.20–1.20]	[0.00–0.40]	
GSI						
Median	0.49	0.81	.069	1.25	0.36	.003*
IQ	[0.16–0.84]	[0.49–1.56]		[0.87–1.60]	[0.21–0.75]	
PST						
Median	18.0	30.0	.018*	30.0	14.0	.025*
IQ	[8.50–28.0]	[22.5–40.0]		20.0–38.0]	[9.0–26.0]	
PSI						
Median	1.36	1.30	.966	1.83	1.30	.001*
IQ	[1.19–1.72]	[1.10–2.09]		[1.53–2.38]	[1.00–1.59]	

*$p < .05$.

Discussion

In this study, BSI-53 showed good reliability with a value of the internal consistency coefficient similar to that reported for the Portuguese population [51]. Results showed that h-ATTR V30M amyloidosis asymptomatic and symptomatic carriers have more psychopathological symptoms than the general population, when BSI global indices (GSI, PST and PSI) were evaluated. Also, median levels of GSI and PST, as well as some of the BSI dimensions (somatization, depression, anxiety and psychoticism), were significantly higher in symptomatic than in asymptomatic carriers, suggesting that disease onset and progression is associated with greater psychological distress. Nevertheless, it is important to verify that not only having already the disease but also being a carrier for h-ATTR V30M amyloidosis is associated with higher vulnerability for psychopathological symptoms. These results are comparable to those found for other chronic diseases [2,52]. In Huntington's disease, a neurological hereditary disease with late onset, similar results were found, with more major depressive disorder and obsessive–compulsive disorder symptoms found in Huntington's disease patients and presymptomatic carriers than in the general population, and psychiatric disorders were more prevalent in mutation carriers than in non-carriers [53].

When sex was considered, our results showed that affected women had higher median values for global BSI indices, and for all other dimensions, except for somatization. Asymptomatic women had significantly higher scores for interpersonal sensitivity and phobic anxiety. These results are in accordance with the known epidemiology of mental diseases, which shows a higher vulnerability, namely for anxiety and depression, in females [54,55]. Results show that women are always at higher risk than men are, either if they are still asymptomatic or already affected.

In this study, all BSI dimensions and global indices correlated positively with duration of the disease. In addition, being symptomatic was a predictor for higher levels in all three BSI global indices, and gender was a predictor for GSI and PST. Similar findings, except for sex, were found in Huntington disease, where disease stage, predicted anxiety, depression and general distress [9].

Having children was also a predictor of higher PSI levels. This may relate to concerns about future generations and to patients' perceptions of their incapacities to raise their children that may impose them an additional and higher stress.

Table 6. Independent predictors of each BSI dimension in h-ATTR V30M amyloidosis.

	Regression coefficient adjusted*	*p* Value	95% CI
Independent predictors of BSI somatization			
Sex (female vs. male)	0.382	.006	0.112–0.652
Professionally active (yes vs. no)	0.584	<.001	0.294–0.873
Marital status (married/living with a partner vs. others)	0.378	.008	0.099–0.656
Age at parent's death (≤14 year vs. others)	−0.457	.013	−0.818 to −0.096
History of psychological/psychiatric problems (yes vs. no)	0.424	.022	0.064–0.784
Psychological/psychiatric problems the year before (yes vs. no)	0.487	.011	0.112–0.861
Independent predictors of BSI obsession–compulsion			
Sex (female vs. male)	0.485	<.001	0.228–0.741
Professionally active (yes vs. no)	0.606	<.001	0.344–0.867
Age at parent's death (≤14 year vs. others)	−0.406	.016	−0.735 to −0.077
Psychological/psychiatric problems the year before (yes vs. no)	0.633	<.001	0.326–0.941
Independent predictors of BSI interpersonal sensitivity			
Sex (female vs. male)	0.442	.001	0.181–0.703
Affected parent sex (father vs. mother)	0.311	.021	0.047–0.575
Age at parent's death (≤14 year vs. others)	−0.541	.004	−0.905 to −0.177
History of psychological/psychiatric problems (yes vs. no)	0.736	<.001	0.436–1.037
Independent predictors of BSI depression			
Sex (female vs. male)	0.377	.013	0.081–0.673
Professionally active (yes vs. no)	0.393	.016	0.074–0.712
History of psychological/psychiatric problems (yes vs. no)	0.664	<.001	0.328–1.000
Independent predictors of BSI anxiety			
Sex (female vs. male)	0.501	<.001	0.255–0.748
Professionally active (yes vs. no)	0.302	.027	0.036–0.569
Perceived life changes imposed by the disease (yes vs. no)	0.280	.024	0.038–0.521
History of psychological/ psychiatric problems (yes vs. no)	0.532	<.001	0.253–0.811
Independent predictors of BSI hostility			
Sex (female vs. male)	0.254	.044	0.007–0.502
Age at parent's death (15–24 year vs. others)	0.371	.010	0.092–0.650
History of psychological/ psychiatric problems (yes vs. no)	0.436	.002	0.165–0.708
Independent predictors of BSI phobic anxiety			
Sex (female vs. male)	0.410	<.001	0.203–0.617
Professionally active (yes vs. no)	0.340	.003	0.119–0.562
Age at time of parent's death (≤14 year vs. others)	−0.474	.001	−0.756 to −0.191
Affected parent sex (father vs. mother)	0.224	.032	0.019–0.428
History of psychological/psychiatric problems (yes vs. no)	0.383	.007	0.106–0.661
Psychological/psychiatric problems the year before (yes vs. no)	0.361	.014	0.075–0.647
Independent predictors of BSI paranoid ideation			
Sex (female vs. male)	0.356	.011	0.083–0.628
Age at parent's death (≤14 year vs. others)	−0.606	.002	−0.986 to −0.226
Affected parent sex (father vs. mother)	0.291	.039	0.015–0.566
History of psychological/psychiatric problems (yes vs. no)	0.951	<.001	0.638–1.265
Independent predictors of BSI psychoticism			
Sex (female vs. male)	0.256	.012	0.057–0.455
Age at parent's death (≤14 year vs. others)	−0.306	.031	−0.583 to −0.028
Affected parent sex (father vs. mother)	0.253	.014	0.052–0.454
History of psychological/psychiatric problems (yes vs. no)	0.596	<.001	0.367–0.824

The subgroup of 19 subjects with no established diagnosis was excluded of this analysis. The variables age (continuous), gender (female/male), professional occupation (non-active/active), marital status (married/living with a partner vs. others), having children (yes/no), affected or asymptomatic-carrier parent (father or mother), age of subjects at time of parent's disease onset (≤14 year, 15–24 year, ≥25 year), age at time of parent's death (≤14 year, 15–24 year, ≥25 year), history of psychological/psychiatric problems (yes/no), psychological/psychiatric problems the year before (yes/no) and perceived life changes imposed by the disease (yes/no) were included in the models.
*$p < .05$.

Impact of a chronic disease on family life and its members is well known. Vamos et al. evidenced how Huntington's disease may impose psychological stress on all members of affected families [17]. Patients with Crohn's disease also had more threatening life experiences and adverse family relations [56]. Our results from the *Family and Personal History questionnaire* show that the disease impose and its continuous presence since very early in subjects' lives. Death or disease onset in one of the parents was frequent in childhood, adolescence or youth. Before the age of 14, 25% of asymptomatic or symptomatic carriers had already lost the affected parent, and around 44% had lived with an affected parent. We could not find any data about children's parental loss in the Portuguese general population. In the USA loss of a parent before 15 years of age occurred in 1–5% [57]. A similar study reports that 4–5% of children in UK and Sweden experienced the loss of a parent before their 18th birthday [58,59]. Assuming these values as a reference, our results are quite impressive.

We also did not find any statistics concerning Portuguese children living with one chronically ill parent. Literature reports that 4–12% of children live in households where a parent has a chronic medical condition [16,60]. In this study, 44% of subjects had lived with a sick parent before turning 15 years of age, which may lead to a higher psychological vulnerability for those children.

A large number of studies have addressed psychopathological issues related to death and chronic illness in a parent

during childhood, adolescence or adulthood [59–63]. Early parental loss and other related traumatic events have been suggested to cause psychological distress later during adult life [12,13,64]; also, adult hostility and depression have been associated to parental loss in childhood [65]. Agid et al. evaluated, in a case-control study, rates of early parental loss due to death or separation under 17 years in patients with major depression, bipolar disorder and schizophrenia. The impact of death was not as striking as the effect of separation, and loss before 9 years had a greater impact [66]. Although, other studies have considered spurious the association between early parental loss and adult depression [64,67], the theme has continued to be a focus of interest in current psychiatry. In our study, parent death between age 15 and 24 years predicted a higher mean PST (more psychiatric symptoms) and age at parent's disease onset under 14 years predicted higher levels at PSI (higher intensity of symptoms). These results point to higher psychopathological distress in subjects that lived parent's disease or death in early years of life, which is, in part, in accordance with other studies.

Although, depression is the most frequently referred psychopathological consequence of parental loss, in this study parental death or disease onset, as well as other early life events, were not associated with higher levels of depression in that BSI subscale.

Neverthless, we found associations with other BSI subscales. Parent's death under 14 years was a predictor for higher somatization, anxiety, phobic anxiety, interpersonal sensitivity, obsession–compulsion, paranoid ideation and psychoticism. Hostility scores were higher in patients aged 15–24 years at parents' death, as well as in subjects reporting life changes related to the disease.

Parental loss during early childhood is reported as having a greater impact in adulthood, than such a loss in adolescence or later childhood [66,68]; however, some research has not confirmed this and pointed to later age losses to be equally important [69]. Our results point to a higher vulnerability to psychopathological symptoms if the death of the parent or the illness onset occurs when he is under the age of 14 or in adolescence.

The participants, who experienced parent's death during their adolescence or youth, have lived for a long time with that affected parent, than those on what parental loss occurred earlier in life. Hence, they may have cumulative traumatic experiences with the parent's disease during childhood and later on with subsequent parental death. Considering the severe incapacity caused by the disease, this implies a great burden upon these children, with actual parental loss because of death or due to disability. These children and other family members may eventually suffer what Boss called "ambiguous loss" [70]. This is a situation where someone significant is perceived as physically present while psychologically absent (because of depression or other disease consequence), or physically absent but kept psychologically present. Adverse parenthood has been reported in families with other incapacitating chronic diseases, namely Huntington disease that shares the mode inheritance and some characteristics (as late-onset, physical deterioration and no cure) with h-ATTR amyloidosisV30M [71].

In subjects who reported psychological problems in the past, these were predictors of somatization, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. Having had past life changes related to family disease was a predictor of higher anxiety.

Our multivariable analysis of BSI dimensions pointed also to the vulnerability of females to psychological problems and for those who are professionally non-active. With regard to gender, this confirms the greater vulnerability of women to psychopathological distress. Those who are professionally non-active are also those who are already sick. Not being able to work means, on the one hand, to be already sick with all its possible limitations, and on the other, the impossibility of a professional achievement. This may imply individual psychological consequences but also financial ones, to the family. In our study, we also searched for psychopathological differences related to sex of the affected parent who became sick or had deceased. A greater risk to psychopathological consequences later in adulthood was shown in literature, when that parent was the mother [66,72–74]. However, others studies have been found to differ from these results. Father's loss was a predictor of later mental health problems and more than doubled the risk for major depression [61,75]. Our results showed that when the mother died before subject's age of 14 years, somatization, interpersonal sensitivity, phobic anxiety, paranoid ideation and PST were higher than in subjects who lost their affected father at the same age interval. A higher risk for depression was not found for that group. Yet, mother's loss was a risk factor for psychological vulnerability in several other domains. Curiously, in subjects that had over 25 years at father's disease onset, all BSI dimensions scored higher compared to those with same age at mother's disease onset. This may mean that in older subjects, father's disease may be associated with adult son's projects failure related to financial reasons and insecurity that may have more importance in older age.

Conclusions

Being a carrier of TTR V30M mutation, whether symptomatic or asymptomatic is associated with more vulnerability to psychopathological symptoms and emotional distress. Independent predictors for BSI global indices and dimensions higher than mean levels in the general population were identified in this population. To be already sick, duration of illness, being woman and having children, all seem to play a major role to have psychopathological symptoms or be more vulnerable to psychological distress. Serious life events related to the disease during childhood and adolescence were important determinants of psychopathological symptoms and emotional distress later in adult life.

Life changes and emotional burden during childhood and youth were related to the familial disease and felt as imposing psychological adaptive needs and pointed to increased

vulnerability to psychological distress and, eventually, psychiatric disease. Depression and anxiety were important psychiatric problems reported by affected subjects and the most often referred.

Factors implied in these subjects psychological distress and psychiatric disorders are certainly multiple, and complex, but some can be recognized. Life events related to the disease that happens early in life, parent's death or parent's disease onset, years of disease and gender seem to be major factors associated with psychological suffering in adulthood.

These patients, their families and at-risk subjects need to be cared for their psychopathological problems and psychological/emotional needs. Children and adolescents need also to be cared, and situations of psychological distress must be identified and mental illness prevented.

Multidisciplinary teams including psychologists and psychiatrists must be available in these populations' medical care and psychosocial support.

Study limitations

Due to the configuration of our sample, our results cannot be generalized to other populations, other TTR pathogenic variants or other types of amyloidosis. The use of BSI also has limitations, as psychiatric diagnoses cannot be made with this inventory. Only facts related to h-ATTR V30M amyloidosis and family history of this disease were considered here as "life events". Other important life events, not taken into account, could have influenced our results. Namely, only disease-onset caused by h-ATTR V30M amyloidosis and death of the affected parent was considered. Further research on these and other factors is still needed.

Disclosure statement

Lopes A. received honoraria from Pfizer for presentations at courses of TTR-related FAP. Coelho T. has received support from Pfizer, Ionis Pharmaceuticals and Alnylan Pharmaceuticals to attend scientific meetings, integrates the speaker's bureau of Pfizer, and received honoraria. Sequeiros, J. received honoraria from Pfizer for presentations on genetic counselling of TTR-related FAP and courses, and for the preparation of leaflets and webinars on genetic counselling. Remaining authors report no conflict of interest.

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Estudo 4

O estudo 4 teve como finalidade responder ao objetivo 4. Foi avaliado de que modo os portadores da “mutação” se caracterizavam em termos de dimensões e estilos de vinculação do adulto. O estudo 4 caracterizou uma amostra mais abrangente, quanto aos estilos de vinculação do adulto, associando essa caracterização a dimensões psicopatológicas dos sujeitos.

Adult Attachment and Psychopathological Dimensions in Subjects with Transthyretin-Related Familial Amyloid Polyneuropathy (TTR-FAP)

Running Title: Adult Attachment and TTR-FAP

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Conflicts of Interest

Lopes, A. received honoraria from Pfizer for presentations at courses of TTR-related FAP. Coelho, T. has received support from Pfizer, Ionis Pharmaceuticals and Alnylan Pharmaceuticals to attend scientific meetings, integrates the speaker´s bureau of Pfizer, and received honoraria. Sequeiros, J. received honoraria from Pfizer for presentations on genetic counselling of TTR-related FAP and courses, and for the preparation of leaflets and webminars on genetic counselling. The remaining authors have nothing to declare.

ABSTRACT

Background: Transthyretin familial amyloid polyneuropathy (ATTR-FAP Val30Met) is a rare, fatal inherited amyloidosis. It is a late onset chronic disease with severe consequences in the individual´s personal, familiar and social life. There is no literature regarding adult attachment in these subjects.

Aims: Study adult attachment dimensions and styles, and evaluate if there was any association with psychopathology.

Methods and Results: Three questionnaires were applied to 129 adults (58 men and 71 women) with ATTR-FAP Val30Met mutation: Adult Attachment Scale-R (AAS-R), Brief Symptom Inventory (BSI-53) and a social demographic questionnaire that included history issues related to biographic events linked to parent´s disease. Statistical analysis were performed (comparisons, correlations, multivariable logistic regression and cluster analysis). Asymptomatic (34) and symptomatic (95) carriers participated; mean age was 37yrs (SD=9.5); 66.7% was married and most (65.1%) worked. BSI global symptom index scored above normal population in 37.2%. Considering AAS-R dimensions, 37.2% scored above general population in anxiety; 51.9% scored under mean level for comfort with depending and for close subscale (49.6%). In cluster analysis, 40% were secure, 39% anxious and 21% avoidant. Anxiety was higher in patients and female. Time of disease was inversely correlated with close and depend (rho=-.326, p=.001; rho=-.209, p=.036). Anxiety dimension highly positively related with all BSI dimensions.

Conclusions: TTR-FAP symptomatic and asymptomatic carriers are more susceptible to have insecure attachment. Although disease play an important role, carrier status is also related to it. Psychopathologic distress was associated. Difficulties in relationships and in seeking for care are expected in these subjects.

Keywords: Adult Attachment dimensions, AAS-R, Hereditary ATTR amyloidosis, BSI, Life-events, Psychopathological symptoms.

List Acronyms

TTR-FAP = Transthyretin-Related Familial Amyloid Polyneuropathy

ATTR-FAP Val30Met = Transthyretin familial amyloid polyneuropathy

BSI = Brief Symptom Inventory

BSI-53 =Brief Symptom Inventory

GSI = Global Severity Index

PSI = Positive Symptom Index

PST = Positive Symptom Total

AAS-R = Adult Attachment Scale-R

EVA =Escala de Vinculação do Adulto

SD = Standard Deviation

IQR = interquartile range

OR = Odds Ratio

CI = confidence Interval

INTRODUCTION

Transthyretin familial amyloid polyneuropathy (ATTR-FAP Val30Met) is a rare and fatal inherited amyloidosis, caused by a protein mutation.(1-3). The disease is transmitted in an autosomal dominant way, with a penetrance that approaches 100% in the areas of higher prevalence (4, 5). Although TTR Val30Met mutation occurs worldwide, one of the largest focus is in the north of Portugal. The age of onset is variable and unpredictable but always occurs after the second decade of life. (4, 6, 7). The mutated transthyretin deposits as amyloid and provokes a clinical picture that is dominated by a mixed sensory, motor and autonomic neuropathy. Clinical presentation also includes severe nephrological, cardiac, ophthalmological, vesical, sexual dysfunction and gastrointestinal symptoms (8-10). Disability, dependence and death occur after a mean duration of 11 years if no treatment is undertaken (11). During the last two decades, liver transplant and tafamidis, a drug that prevents mutated protein deposition, became available treatments for this disabling disease. These treatments slow down the disease progression and improve patients´ survival (12-16). However, for a long time, these patients and their families lived with a disease that had no treatment and they had to face a chronic and catastrophic clinical evolution. Depression and anxiety were found to be the most relevant symptoms reported in a liaison psychiatry consultation in a preliminary study that included 30 TTR-FAP patients (17).

Asymptomatic and symptomatic carriers of ATTR FAP Val30Met have preserved fertile years. Women have children during longer time due to the slightly later onset of disease compared to men (4).Disease onset, often in mid 20s to mid-30s, and its progression even when available treatments are delivered, may imply that these families with young offspring have to deal with one parent´s death or live with one sick parent and with all the psychological, familial and social implications of this.

Parenting may be affected when a parent is affected by a chronic illness, either because it provokes physical limitations but also depression or other emotional distress (18, 19). This may imply less availability for parenthood (20, 21). In these affected families, disturbs in couple´s relationship may also happen(22).

To study psychological aspects in subjects with TTR-FAP, which may affect individual coping with the disease and family dynamics, we chose attachment theory as a theoretical framework. According to Bowlby´s attachment theory (23-25), human new-borns have, an instinctual need and capacity to seek proximity to the caretaker and make close emotional bonds. In the course of child/parent interactions, cognitive and affective internal constructs develop. These are referred as working models, the individual´s internal representations of world and of significant people within it, including the self (24), that are present across lifespan and constitute the foundation of attachment.The attachment system serves as a mechanism for survival and it is active in situations where danger or vulnerability are present.

The attachment will be secure when the caregiver (mother, father or other person) responds adequately to the child´s needs. If the child´s needs are not met, the attachment representation will be insecure, which can provoke increasing vulnerability to major problems later in life, regarding relationships with others or emotional distress. The nature and quality of this early relationship will depend on caregiver´s availability and responsiveness to the child´s needs. These attachment representations will serve as working models in social relationships throughout life.

Attachment is also a theory of the lifespan development of close relationships. As adults, healthy human beings continue to rely on intimate relationships to overcome vulnerability or danger(24).Adult attachment is defined as an emotional bond to another person, which cannot be replaceable by any other, although there may be more than one such a person(26, 27). Adult attachment has been largely studied: how it relates with early attachment(28), with

psychopathology or emotional distress(29, 30), and how it expresses the capacity for intimacy in romantic love(31). Adult Attachment has also been studied in patients with medical illnesses searching to understand if and how it relates with symptomatic expression and how it influences doctor–patient relationship (32-34).

Adult Attachment has been studied in individuals with Huntington Disease, a neurogenetic late onset disease. Using Adult Attachment Interview, authors concluded that these subjects had lower percentage of secure attachment representations and higher unresolved/disorganized representations associated with the death of the sick parent before 18th birthday (35).

In a previous exploratory research on this topic, adult attachment has been studied in TTR-FAP patients(36). The study showed that TTR-FAP patients had more problems on adult attachment dimensions depending and comfort with closeness, when compared with a control group.

The aim of the present study was to evaluate Adult Attachment in ATTR-FAP Val30Met symptomatic and asymptomatic carriers, compare them with general population and assess correlations between adult attachment and psychopathological dimensions.

METHODS

Participants

The study sample included 129 adults (58 men and 71 women) with ATTR-FAP Val30Met mutation regularly followed in an outpatient unit. Ninety-five participants (74%) were TTR-FAP patients and 34 (26%) were asymptomatic carriers. All subjects aged 18 to 65 years were eligible to be included in the study. Participants were recruited at their routine consultation and agreed to answer the study questionnaires. All procedures performed were approved and in accordance

with the ethical statements of the institutional Ethical Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All study participants signed a written consent.

Instruments

Three questionnaires were applied: AAS-R or EVA -*Escala de Vinculação do Adulto,* according to Portuguese translation,BSI-53 and a social demographic questionnaire that included questions addressing biographic events related to parent´s disease and death.

The AAS-R is an evaluation scale that assesses attachment dimensions in adults (37). It is a self-report measure of feelings and perceptions of adult relationships. It consists of a self-rated questionnaire with 18 items answered on a 5-point Likert –type scale. It has three subscales that evaluate three attachment dimensions: close, depend and anxiety. Close dimension evaluates how comfort the person feels with closeness and intimacy. Depend dimension evaluates discomfort to getting close and with depending on others whenever needed and anxiety dimension measures how preoccupied one may feel about being rejected or abandoned. These dimensions, according to literature, can be associated to adult attachment styles as described by Hazan and Shaver (31, 37, 38): secure, avoidant and anxious. The AAS-R was translated and validated for Portuguese population by Canavarro (39, 40).According with this study validation, the mean values of the three dimensions obtained for Portuguese population were: 3.49 (SD= 0.58) for *Close subscale*; 2.43 (SD=0.74) for *Anxiety subscale;* and3.27 (SD=0.53) for *Depend subscale*.

The BSI-53 is a screening tool used for detecting psychopathological symptoms. These may be indicators of emotional distress. It consists of a self-rated questionnaire with 53 items that are answered on a 5-point Likert-type scale-ranging zero (not at all) to four (extremely). The BSI-53 has nine subscales, which assess nine domains of psychopathology: Somatization,

Obsessive–Compulsive, Interpersonal sensitivity, Depression, Anxiety, Anger–Hostility, Phobic anxiety, Paranoid ideation, and Psychoticism. Three global indices of distress were computed: Global Severity Index (GSI), Positive Symptom Index (PSI), and Positive Symptom Total (PST). GSI represents a combined assessment of intensity of distress and the number of symptoms; PSI gives a media of intensity for all symptoms and PST represents the number of signalized symptoms. Derogatis developed the BSI in 1982 (41, 42). The validated Portuguese version of BSI-53 was used in this study (43). The mean values of global indices obtained for Portuguese population were 0.83 (SD=0.48) for GSI, 26.99 (SD=11.72) for PSI and 1.56 (SD=0.38) for PST.

Subjects fulfilled the protocols in the presence of the same investigator, who assisted in the process of filling and solving doubts that respondents might have.

Statistical analysis

Preliminary tests for normal distribution, outliers and missing data were conducted.

Data were non-normally distributed for all three EVA dimensions. Several attempts were done to normalyze data without success, thus non-parametric tests were used in most of the analysis. Accordingly, the results are mainly expressed as the median and interquartile range (IQR) for continuous variables, or mean and standard deviation (SD) for comparing with Portuguese mean values. Categorical variables are expressed as absolute and relative frequencies.

Cronhbach's alpha statistics measured internal consistency of the EVA-18 scale as a whole and each of its three subscales. Guttman split-half statistic further evaluated the EVA internal reliability.

Comparisons between continuous variables were done using non-parametric Mann-Whitney test and Kruskal-Wallis test. Comparisons between categorical variables were made

using chi-squared test. Correlations with and among the EVA scales were computed Spearman correlation.

Univariable logistic regression was used to analyse the association between EVA styles and BSI global indices dichotomized according to mean Portuguese values. Multivariable logistic regression analyses (backward method) were done to identify the factors that were independently associated with values of anxiety, close and depend subscales higher than the mean levels achieved for Portuguese population. Covariates considered for selection in this analysis were chosen based on their significance in univariate analysis or by their clinical relevance. Cluster analysis (K-means) was performed using the three attachment dimensions (close, depend and anxiety) to define 3 attachment styles.

The level of statistical significance was set at 0.05 with 95% confidence intervals. All of the analyses were performed using IBM SPSS Statistics software, version 23.

RESULTS

The descriptive analysis of the sample (N=129) is displayed in Table 1.

BSI-53 global indices (GSI, PST and PSI)

The mean GSI score was 0.797 (SD=0.67), median = 0.60. Considering the mean levels of Portuguese general population (Canavarro, 2007), 37.2% of total sample were above the mean levels for general population (mean=0.83, SD=0.48). Considering the subgroups, 20.6% of non-symptomatic carriers and 43.2% of patients were above mean levels of GSI. The mean PST levels for the global sample were 23.96 (SD= 14.58), median = 23.0, and 41.9% were above mean levels for general population (mean=27.0, SD=11.7). Considering the subgroups, 26.5% of non-symptomatic carriers, and 47.4% of patients were above mean levels of PST. The mean PSI scores for the total sample were 1.56 (SD=0.54), median=1.46, and 39.5% were above mean levels for

general population. Considering the subgroups of subjects, 20.6% of non-symptomatic carriers, and 46.3% of patients were above mean levels of general population.

Adult Attachment Scale Reliability: Internal consistency

The total EVA score demonstrated an acceptable reliability (Cronbach's α =0.71; Guttman split half reliability = 0.77). The internal consistency of the three subscale scores was examined by using Cronbach's alpha. The higher Cronbach's alpha was 0.82 for anxiety, lower values of 0.54 were achieved for the Close, and Depend subscales. These results were similar to those reported by Canavarro (39) in their study performed to validate EVA in a community Portuguese sample.

EVA Dimensions

The mean "comfort with closeness" (*Close subscale*) score for the global sample were 3.52(SD= 0.63, median = 3.5), and 49.6% were under mean levels for general population (mean=3.49). Considering the subgroups 41.2% of asymptomatic carriers and 52.6% of TTR-FAP patients were under mean levels.

The mean "anxiety" *(Anxiety subscale)* score in this sample was 2.14 (SD=0.80, median = 2.0). Considering the mean levels of Portuguese general population (39), 37.2% were above the mean levels for general population (mean=2.43). When the subgroups of subjects were evaluated, 29.4% of asymptomatic carriers and 40.0% of TTR-FAP patients were above mean levels.

The mean "comfort with depending on others" *(Depend subscale)* score for the total sample was 3.15 (SD=0.67, median = 3.16) and 51.9% were under mean levels for general population. Considering the subgroups of subjects, 38.2% of asymptomatic carriers and 56.8 % of TTR-FAP patients were under mean levels of general population.

EVA dimensions comparisons

Subgroups: asymptomatic carriers' vs TTR-FAP patients

Levels of *anxiety* and *comfort with closeness* were respectively lower and higher in asymptomatic carriers comparing to TTR-FAP patients, but these differences were not statistically significant. In relation to depend dimension (*comfort with depending on others)*, significant higher levels were found in asymptomatic carriers comparing to TTR-FAP patients (Table 2).

Gender

Considering the global sample, anxiety median scores were significantly higher in female vs. male (2.33 vs. 1.83, p= .004). After stratifying by subgroups, the significant differences between female and male remained in TTR-FAP patients (2.50 vs. 1.83, p= .003), but no significant differences in anxiety scores were found in asymptomatic carriers. Regarding Close and Depend subscales, no significant differences were found between male and female in global sample and in the subgroup of asymptomatic carriers. Considering the TTR-FAP patients subgroup, female had lower scores of Close and Depend subscales, comparing to male patients (3.33 vs. 3.58, p= .080; 3.00 vs. 3.33, p=.083).

Other comparisons

Differences, although not significant, were found in anxiety, close and depend subscales, regarding: age of subjects at time of parent´s disease onset (<14yr, 14-24 yrs., ≥ 25 yrs.), age at time of parent´s death (<14yr, 14-24 yrs., ≥ 25 yrs.), and the sick parent (mother or father).

Correlations with EVA dimensions (age, time of disease and BSI)

In the global sample, no correlation was found between age and any of the EVA subscales.

In TTR-FAP patients, the evolution time of the disease was inversely correlated with close and depend dimensions (respectively, rho= -.326, p= .001; rho= -.209, p= .036), but not with anxiety.

The correlation matrix between BSI and EVA dimensions was made. In summary, anxiety dimension evaluated by EVA is positively correlated with all BSI dimensions and global indices and the best *correlation* is between BSI interpersonal sensitivity and anxiety (rho= .557, p<.001). Negative and not so strong correlations were obtained for Close and Depend subscales with all BSI dimensions and indices (Table 3).

Independent predictors of Anxiety, Close and Depend subscales

Multivariable logistic regression analyses were done to identify the independent predictors of anxiety, close and depend subscales higher than the mean levels achieved for Portuguese population. The variables age (categorical higher or under 35 yrs.), gender, subgroup (asymptomatic carrier or TTR-FAP patient), sick parent (father or mother), age of subjects at time of parent´s disease onset (<14yr, 14-24 yrs., ≥ 25 yrs.), age at time of parent´s death (<14yr, 14-24 yrs., ≥ 25 yrs.), having children (yes/no) and marital status (single, married, others) were tested.

The independent predictors of anxiety that score > 2.43 were: female vs. male gender (OR=2.49, p= .021, CI 95% 1.149-5.392), age ≤ 35 yrs. vs. > 35 yrs. (OR=2.17, p= .049, CI 95% 1.004-4.706), and symptomatic patients vs. asymptomatic carriers (OR=2.24, p= .083, CI 95% 0.904-5.554).

No independent predictors were identified of close subscale score higher than 3.49.

The independent predictors of depend that score > 3.27 were: male vs. female gender (OR=2.46, p=.016, CI 95% 1.184-5.134) and asymptomatic carriers vs. symptomatic patients (OR=2.49, p= .032, CI 95% 1.080-5.74).

Attachment styles

Cluster analysis (K-means) was performed using the three attachment dimensions (close, depend and anxiety) to define the clusters. The results were consistent with the three attachments styles from Hazan e Shaver (44) and also performed by Canavarro in Portugal (2006). An individual with secure attachment style was comfortable with closeness, able to depend on others, and not worried about being abandoned or unloved. An avoidant individual was uncomfortable with closeness and intimacy, not confident in others' availability, and not particularly worried about being abandoned. Finally, an anxious person was comfortable with closeness, confident in the availability of others, but very worried about being abandoned and unloved (38).

Considering all sample, 40% of subjects were classified as secure, 39% as anxious and 21% as avoidant. Anxiety is the dimension with more weight in forming the clusters ($F_{(2,126)}$=125.01; p<.001). The attachment styles of the global sample are described in table 4.

Comparisons between subgroups were performed. Secure style was more frequent in asymptomatic carriers and avoidant style in FAP patients (table 5).

Comparing BSI anxiety and depression according to EVA style attachments, the secure style presented the lower median levels and the anxious style the higher median levels (table 6).

Association between EVA styles and BSI global indices

Considering the mean values of BSI global indices obtained for Portuguese population, BSI levels were dichotomized and used as dependent variable in univariable logistic regression. EVA styles were included as an independent variable, considering Secure style as reference.

The Anxious and Avoidant styles were significantly associated with values of GSI higher than 0.83 (OR=9.8, p<.001, CI 95% 3.5-26.9 and OR=8.2, p<.001, CI 95% 2.6-25.7, respectively); with PST higher than 26.99 (OR=11.5, p<.001, CI 95% 4.1-31.9 and OR=15.3, p<.001, CI 95% 4.7-49.3, respectively); and with PSI higher than 1.56 (OR=5.3, p<.001, CI 95% 2.2-12.9 and OR=3.9, p= .009, CI 95% 1.4-10.8, respectively).

DISCUSSION

Considering psychopathological dimensions, results from BSI showed that percentages ranging from39,5% to 41,9%, of global sample, were above mean levels found by Canavarro for general population in GSI, PST and PSI dimensions (43). The symptomatic and asymptomatic groups demonstrated, in a considerable number of subjects, more psychopathological symptoms than general population. These results point to the existence of high levels of psychosocial distress in this specific population. When the two subgroups were compared, it was noticed that the group of patients had higher levels for psychopathological symptoms

Results of present study indicate that Portuguese subjects with ATTR-FAP Val30 Met have different distribution patterns of Adult Attachment dimensions when compared with normal population evaluated by Canavarro(39). Although the mean score for close dimension was higher than the normative, almost half of the sample scored lower than normative. When subgroups were compared, almost half of patients' subgroup were under mean levels.

When anxiety subscale was evaluated (anxiety dimension), our sample had more

subjects scoring above the mean values than general population, and again, even more subjects of the patients´ subgroup scored also higher. Finally, for "comfort with depending on others" (Depend dimension), more than half of ATTR-FAP Val30Met subjects scored under normative scores for Portuguese population. When the scores of subgroups were compared, more subjects who were already ill scored that way.

From the cluster analysis, we concluded that although secure style was the most represented, anxious style was present in a high percentage of subjects as well as avoidant attachment. Most of total sample had anxious or avoidant styles of attachment. This distribution differs from that found by Shaver for general population, in which secure attachment was predominant, and anxious the less represented (45).

In our sample, female gender was associated with significant higher scores of anxiety in sick women and lower scores in close and depend dimensions. This was not according to original measures of Adult Attachment based on the three attachment prototypes that appeared to be unrelated to gender (31, 46, 47). However, subsequent evaluations suggested that males had more dismissing attachment style and women showed greater comfort with closeness and preoccupation with relationships. This could be more in agreement with the findings of the current study for this population.

Adult attachment may reflect experiences prior to adulthood, rooted in infancy and early childhood, presumed to be determined by caregiver´s availability and responsiveness to the child´s needs (23, 38).

As we knew that a considerable number of symptomatic and asymptomatic carriers had lost one of their sick parent or had lived with one during childhood or youth, comparisons were made between these and the other subjects to whom such events had not occurred.No significant differences were found for adult attachment dimensions considering subject´s age

(childhood or youth) at parent´s disease or death.

Although we could expect that these sick parents could influence attachment in infancy, the illness or death of parent during childhood, adolescence or youth was not found to be a predictor of insecure dimensions of adult attachment in this population. In the same way, there were no significant differences in attachment dimensions when we compared the subjects that had lost a parent or had lived with a sick one in childhood or youth, with the subgroup of subjects to whom such events had not happen. It could be thought that in a disease in which the hereditary character is so determinant and long lasting, families could adapt themselves to expected losses and manage to organize family support that to compensate for the lack of one of the parents. On the other hand, the small size of these subgroups could explain these results and this issue remain to be further clarified.

Adult Attachment defines one´s way of forming close relationships with other adults, and the attachment experience should find expression in adult´s attachment style (44). Secure attachment means that a person gets involved in close relationships, has few problems with mutual dependency and is not afraid of being abandoned (31, 38).

Some specificity of emotional distress symptoms and adult attachment dimensions have been established (29). Adult attachment insecurity was associated with self-reports of psychiatric symptoms especially in individuals experiencing high levels of life stress(48).In this population we found a clear association between anxiety and depend dimensions in EVA and psychological distress expressed by global BSI indices. Anxiety and depend dimensions were also associated with BSI anxiety and depression dimensions.

According to Kobak (49) Adult Attachment self-reports are associated with interpersonal behavior mostly under conditions of attachment–related threat, in emergency conditions . This could explain why being sick was the most important predictor for insecure patterns of adult

attachment found in the present sample. Suffering the disease progression, the threats of functional, personal, affective losses, could constitute a long-lasting danger influencing the way in which these subjects live relationships. TTR-FAP symptomatic patients had also higher levels of psychopathological symptoms which could explain the insecure attachment patterns and be associated with the high levels of stress associated with a disease that provokes loss of autonomy, self-image disturbances, functional losses and social losses. Besides, these losses are experienced not only as actual losses but also as expected ones, given the progressive character of the disease. This means that these subjects have permanent doubts about the future, about when and how symptoms and its consequences will happen which represents a permanent threat impending upon their lives.

Although being sick has been, in our study, the most relevant aspect associated to insecure dimensions of adult attachment a relevant percentage of asymptomatic carriers also scored higher than normal population in insecure dimensions. In this subgroup, the uncertainties regarding the future and the finding of being a carrier of a genetic disease remain important issues that may influence how they relate to others and how they see themselves. Having a genetic mutation that will provoke a disease, which in many cases is already known, may alter the self-perspective these subjects have, and influence how they expect to be seen by others. This could lead to insecure ways of making relationships with others, with an important anxiety dimension in adult attachment.

Although attachment patterns may change, in first place, if there is disturbances in the quality of interactions between caretaker and the child, in adulthood, the influence of new emotional relationships may alter the attachment patterns. Paying attention and treat the difficulties in adult relationships that TTR-FAP carriers may have, even when they are still asymptomatic, may improve their emotional capacities and quality of life and reduce psychopathological events.

Difficulties in adult relationships in these populations, mostly express fear of being abandoned or problems in trust others and fear of depending. This is an important issue as it may lead to more difficult relationships between these individuals whether with their peers and relatives or with health personnel. In a significant group of these subjects, such problems are associated with psychopathological distress and certainly may influence attachment with next generations.

CONCLUSIONS

Adult attachment dimensions differ from normal population distribution in symptomatic and asymptomatic carriers of ATTR-FAP Val30Met Portuguese patients. Many people with the mutation, but even more when they are already sick, score higher in anxiety and comfort with depending.

Anxious style of attachment is highly represented either in asymptomatic or symptomatic carriers. With regard to avoidant style of attachment, it characterized a significant number of patients.

Psychopathological dimensions and particularly depression and anxiety are related to insecure attachment in Portuguese TTR-FAP carriers whether symptomatic or asymptomatic.

This implies that a special attention to the way these subjects seek for medical or social help, how they structure their relationships with other adults and their offspring. To care for these populations, there must be multidisciplinary teams where psychosocial care is available.

Finally, in these populations, special attention must be paid to the presence of psychological distress or psychopathological conditions requiring treatment.

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Table 1- Descriptive analysis of total sample (N=129)

	Study Sample			
	n	*%*	*M (SD)*	*Min-Max*
Age				
Study sample	129		37 (± 9)	21-66
Asymptomatic carriers	34	26.4	32 (± 9)	21-61
TTR-FAP patients	95	73.6	38 (± 8)	24-66
▪ Years of disease	95		7.0 (± 6.9)	1-28
Sex				
Female	71	55		
Male	58	45		
Marital Status				
Single	30	23		
With partner	11	9		
Married	75	58		
Widowed	1	1		
Divorced	12	9		
Children				
Yes	80	62		
No	49	38		
Number of Children				
1	52	40		
2	22	17		
3	5	4		
4	1	1		
No children	49	38		
Schooling Level				
4 years of schooling	15	12		
5 – 6 years of schooling	32	25		
7 – 9 years of schooling	22	17		
High School (12 years of schooling)	30	23		
University Degree	29	22		
Illiterate	1	1		
Professional Situation				
Active	84	65		
Retired	13	10		
Sick Leave	6	5		
Unemployed	26	20		

Table 2 – Comparisons of EVA dimensions in subgroups

	Asymptomatic carriers Median [IQR]	**TTR-FAP patients** Median [IQR]	***P value***
Anxiety (Anxiety subscale)	1.92 [1.17-2.54]	2.17 [1.67-2.67]	0.186
Comfort with closeness (Close subscale)	3.67 [3.17-4.04]	3.33 [3.00-4.00]	0.117
Comfort with depending on others (Depend subscale)	3.42 [2.83-3.71]	3.17 [2.67-3.67]	**0.040***

[IQ] – Interquartile range *P<0.05. Comparisons were made using Mann-Whitney test.

Table 3 - Correlations matrix between Brief Symptom Inventory (BSI-53) dimensions and Adult Attachment Scale-R (AAS-R)

		Anxiety Dimension	Close Dimension	Depend Dimension
Somatization	*r*	0,407**	0,275**	- 0,347**
	p	0,000	0,002	0,000
Obsessive-Compulsive	*r*	0,412**	- 0,343**	- 0,367**
	p	0,000	0,000	0,000
Interpersonal Sensitivity	*r*	0,561**	-0,415**	- 0,325**
	p	0,000	0,000	0,000
Depression	*r*	0,485**	-0,369**	-0,384**
	p	0,000	0,000	0,000
Anxiety	*r*	0,483**	-0,283**	-0,319**
	p	0,000	0,001	0,000
Anger-Hostility	*r*	0,399**	- 0,223*	-0,368**
	p	0,000	0,011	0,000
Phobic Anxiety	*r*	0,456**	-0,306**	-0,338**
	p	0,000	0,000	0,000
Paranoid Ideation	*r*	0,465**	-0,284**	-0,377**
	p	0,000	0,001	0,000
Psychoticism	*r*	0,461**	-0,387**	-0,411**
	p	0,000	0,000	0,000
Global Severity Index (GSI)	*r*	0,509**	-0,369**	-0,415**
	p	0,000	0,000	0,000
Positive Symptom Total (PST)	*r*	0,500**	-0,397**	-0,409**
	p	0,000	0,000	0,000
Positive Symptom Index (PSI)	*r*	0,369**	-0,199*	-0,319**
	p	0,000	0,024	0,000

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 4 - Cluster of the Attachment Styles

	Anxious (n=50)	**Avoidant (n=27)**	**Secure (n=52)**	**F (2, 126)**
Close	3.42	3.08	3.86	18.45*
Depend	3.08	2.36	3.64	64.68*
Anxiety	2.94	1.93	1.50	125.01*

*P<0.001 using K-means cluster analysis

Table 5 – Comparison of attachment styles between asymptomatic carriers and FAP patients

	Asymptomatic Carriers (n %)	**ATTR-FAP Patients (n, %)**	***P value***
Anxious	13 (38)	37 (39)	
Avoidant	1 (3)	26 (27)	0.04*
Secure	20 (59)	32 (34)	

*P<0.05. Comparisons were madeusing chi-squared test

Table 6 – Comparisons in BSI anxiety and depression according to EVA styles

	Anxious	**Avoidant**	**Secure**	*P-value*
	Median [IQ]	Median [IQ]	Median [IQ]	
BSI Anxiety	0.83 [0.50-1.50]	0.83 [0.33-1.17]	0.25 [0.10-0.50]	<0.001*
BSI Depression	1.33 [0.50-2.00]	1.00 [0.33-1.83]	0.17 [0.10-0.33]	<0.001*

*P<0.05. Comparisons were made using Kruskal-Wallis test

Estudo 5

O estudo 5 teve como finalidade prosseguir os objetivos dos pontos 5 e 6. Foram realizados 3 estudos complementares, em que foi avaliado o funcionamento familiar percebido em termos de coesão, flexibilidade e comunicação. No primeiro, foram avaliados portadores sintomáticos e assintomáticos de PAF, tendo sido comparados estes dois grupos; no segundo, a mesma metodologia foi aplicada a portadores da mutação e respetivos cônjuges, sendo os dois grupos comparados; no terceiro, foram avaliados e comparados, com a mesma metodologia, doentes com PAF e um grupo emparelhado de doentes com esclerose múltipla.

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WILEY CLINICAL GENETICS

ORIGINAL ARTICLE

Family dynamics in transthyretin-related familial amyloid polyneuropathy Val30Met: Does genetic risk affect family functioning?

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Adult-onset, chronic, genetic diseases like transthyretin-related familial amyloid polyneuropathy Val30Met (TTR-FAP Val30Met), have a major psychosocial impact not only on patients, but also on families. Genetic risk may therefore be an increased factor in psychosocial impact of the disease on these families' functioning. To evaluate impact of genetic risk, a study was conducted to perceive the impact of the illness on families' functioning. Groups of TTR-FAP Val30Met patients, pre-symptomatic carriers, partners and patients with multiple sclerosis (MS), a non-hereditary disease, were studied. Sample included 190 adults: 87 patients and 28 pre-symptomatic carriers for TTR-FAP Val30Met, 41 partners and 34 patients with MS. Family Adaptability and Cohesion Scale IV (FACES IV) and a social-demographic questionnaire were applied. No significant differences were observed between patients and pre-symptomatic carriers and both these and their partners regarding cohesion and flexibility. MS patients scored significantly higher in median scores for balanced scales. Satisfaction and communication levels were also lower in patients with TTR-FAP Val30Met than with MS. Family functioning was perceived as balanced by most TTR-FAP Val30Met patients and pre-symptomatic carriers. These families may be considered as mostly healthy. Difficulties in family communication should be taken into account when caring for these families.

KEYWORDS
ATTR amyloidosis V30M, FACES IV, family systems, TTR-FAP Val30Met

1 | INTRODUCTION

Severe chronic diseases have a major psychosocial impact on patients, as well as on their families. In transthyretin (TTR)-related familial amyloid polyneuropathy (FAP) Val30Met (also known as ATTR amyloidosis V30M), which is inherited as an autosomal dominant condition, the psychosocial impact resulting from the risk that several other close relatives may become ill is a significant additional burden.

Huntington disease (HD) is an autosomal dominant neurological disease, which has similar features (adult-onset, severity, disability) with TTR-FAP Val30Met. Vamos et al evidenced how HD may impose psychological stress to all members of affected families. A high rate of family dysfunction was reported in patients with HD.[1] Sobell emphasized how HD forced them to cope with disturbing events and untimely deaths; if some families were able to make healthy transitions, other became blocked and dysfunctional.[2] A model has been proposed to address the specific psychosocial impact of chronic genetic diseases in families taking into account the pre- and post-diagnosis phases and how they relate to family life-cycle and functioning.[3]

The most burdensome aspects of caring for HD patients were negative experiences with health and social care, dissatisfaction with carers' role, concern over children, family breakdown, and loss of social contact and of meaningful relationships. Differences from other neurodegenerative diseases included the early adulthood-onset, severity and hereditary transmission of HD.[4]

TTR-related FAP Val30Met is a rare and fatal, systemic form of disease, caused by the extracellular deposit of amyloid.[5–7] It is inherited as an autosomal dominant condition, its penetrance approaching 100% that is different and higher than in other countries, for example, Sweden. It occurs worldwide, but has major clusters in Portugal, Sweden and Japan.[8,9] Age-of-onset is variable and unpredictable, but usually after the second decade of life.[8,10–13] Its clinical picture is dominated by a severe sensory-motor and autonomic neuropathy, but includes also system and organ failure; it causes great disability, dependence and death after a mean duration of 11 years.[14] Liver transplant and tafamidis, a drug that kinetically stabilizes the tetrameric TTR and prevents amyloid deposits, are current accepted treatments to slow-down disease progression[15–18] Although still an incurable disease, and in spite that only some patients (in the early disease stage of the disease) do benefit from these treatments, this establishes a significant difference form HD and other late-onset neurological diseases.

Given the familial nature and late onset of TTR-FAP Val30Met, it could be expected that family members may have to adjust the way they relate to each other, with an impact in the family system. Transitions due to the disease (becoming ill, awareness of genetic status, marriage, having children) may become factors of imbalance for patients and the whole family system.

There are very few family studies on this TTR-FAP Val30Met. A study in family dynamics was conducted in a group of "at risk" relatives whilst waiting for genetic testing.[19] It concluded that these families were highly flexible and, when unbalanced, tended to be chaotic; satisfaction with family functioning was low. In order to understand the experiences lived by family members, a phenomenological study was conducted in Sweden, where members of six families were interviewed. Two major themes emerged: the difficulty and the need to accept a disease with such serious implications for the lives in the whole family.[20]

A study of Portuguese TTR-FAP Val30Met patients on transgenerational aspects of the illness to understand the role of older generations has shown that there was an intergenerational flow of support, and that communication was higher among affected members and between mothers and affected daughters.[21]

The aims of this study were to (1) evaluate how TTR-FAP Val30Met affected patients and pre-symptomatic carriers perceive their family´s functioning, (2) compare the perception of the family system by these two groups to that of their partners, and (3) compare the above mentioned perceptions to those of patients with multiple sclerosis (MS).

2 | METHODS

2.1 | Participants

The study included an unselected sample of 87 adult patients with TTR-FAP Val30Met, 28 pre-symptomatic carriers, 41 partners, and, as a control group, 34 patients with MS of the relapsing-remitting type with an EDSS (Expanded Disability Status Scale) score below 4.5.

All subjects aged 18 to 65 years were eligible. Participants were recruited consecutively between 2014 and 2015, when coming to their routine consultations at our Reference Centre; partners were invited whilst accompanying patients to appointments. All agreed to answer the study questionnaires. Stage of the disease was not an exclusion factor. MS patients were then paired with stage 1 TTR-FAP patients, according to sex, age and marital status (EDSS score in MS and stage of TTR-FAP chosen to include patients with minor motor dysfunction only).

All procedures were in accordance with the institutional ethical statements and the Helsinki declaration (1964 and its later amendments); the study was approved by the CHP Ethics Committee. A single researcher approached all participants about the study and presented them the instruments; all gave their written consent.

2.2 | Instruments

The Family Adaptability and Cohesion Scale IV (FACES IV) and a social-demographic questionnaire were applied to all participants.

FACES IV is based on the The Circumplex Model of Marital and Family Systems, developed by Olson et al.[22] It describes family functioning using three key concepts: cohesion, flexibility and communication[23–25]; it has been used for clinical and research purposes. *Cohesion* is defined as the emotional bonding that family members have toward one another; it is classified as disengaged, separated, connected or enmeshed.[26] *Flexibility* is the quality and expression of leadership and organization, roles, relationship rules and negotiations[27]; it is categorized as chaotic, flexible, structured or rigid.[26] *Communication* is defined as the positive communication skills used in family system or couple[26]; high communication levels in the family facilitate changes needed and lead to a better cohesion and flexibility.

FACES IV is a self-rated questionnaire with 62 items, answered on a 5-point Likert scale, that has two balanced scales (cohesion and flexibility) assessing central-moderate areas, and four unbalanced scales (enmeshed and disengaged; rigid and chaotic) assessing more extreme dimensions. It also provides ratio scores (cohesion, flexibility and total), which measure the level of balance vs unbalance in the family system. The model's main hypothesis is that balanced levels of cohesion and flexibility are most conducive to healthy family functioning, while unbalanced (low or high) levels of cohesion and flexibility are associated with dysfunctional family functioning.[27,28] The mid-range typology characterizes families that did not score high neither in balanced nor in unbalanced scales; they have a moderate level of functioning and do not have high levels of strength or protective factors.[29] The four scales were found to be reliable and allow for discriminating problematic from non-problematic families.[27] We used the Portuguese translation of FACES IV, authorized by the authors, and previously used in families with a schizophrenic parent.[30] FACES IV was validated for a Portuguese sample of oncologic patients´ carers.[31]

A social and demographic questionnaire was specifically constructed, to acquire data on disease status (affected patient or pre-symptomatic carrier), age, sex, marital status, number of children, education level and employment status.

2.3 | Statistical analysis

Preliminary tests for the Normal distribution, outliers and missing data were conducted. The Kolmogorov-Smirnov test was used to evaluate distribution of continuous variables. Quantitative values are expressed as mean ± SD, or median with interquartile range (IQR) if the variables did not follow the Normal distribution. Categorical variables are reported as proportions. Data were asymmetrically distributed for all FACES IV scales and ratios; thus, non-parametric tests were used in most analyses. The Mann-Whitney *U* test was used to compare quantitative variables between two groups. The level of statistical significance was set at 0.05, with 95% confidence intervals. All analyses were performed using the IBM Corporation. SPSS Statistics for Windows, version 23.0. Armonk, New York.

3 | RESULTS

3.1 | TTR-FAP Val30Met patients vs pre-symptomatic carriers

We first studied 115 subjects carrying the TTR-FAP Val30Met variant (67 females and 48 males): 28 were still asymptomatic, while 87 were already affected. Social and demographic variables are described in Table 1.

3.1.1 | Scales scores and graphical representation of FACES IV

On the two balanced scales, most pre-symptomatic carriers rated their families as *very connected* (54%) or *connected* (46%), 68% as *flexible*, 18% as *very flexible* and 14% as *somewhat flexible*. On the four unbalanced scales, most reported *very low* scores: 93% disengaged, 75% enmeshed, 75% rigid and 93% chaotic; one pre-symptomatic carrier scored family as *high* for the rigid dimension (Figure 1).

Patients rated their families as *connected* (49%) or *very connected* (44%), 64% as *flexible*, 21% as *very flexible* and 15% as *somewhat flexible*. On the four unbalanced scales, most patients reported *low* or *very low* scores (96% disengaged, 91% enmeshed, 88% rigid, 96% chaotic); 1% of patients perceived their family as having a *high* score for the rigid dimension, 1% rated it *high* for disengaged, 1% for enmeshed and 1% for chaotic dimensions (Figure 1).

3.1.2 | Scales and ratios comparisons

Pre-symptomatic carriers had a median score of 68.0 for balanced cohesion and 59.0 on the balanced flexibility scale. Patients had a median score of 65.0 for balanced cohesion 55.0 for balanced flexibility. Unbalanced disengaged, enmeshed and rigid scales had higher scores in patients vs carriers (15.5 vs 16.0; 18.0 vs 20.0; and 22.0 vs 26.0). In the chaotic scale, the median is the same (15.0). No significant differences were found between both groups.

Median cohesion, flexibility and total ratios were higher in pre-symptomatic carriers (3.8 vs 3.1, 2.7 vs 2.5 and 3.6 vs 2.8), but differences were not significant.

3.1.3 | Comparison of communication levels

Communication level was *high* or *very high* for 68% of patients and 61% of carriers. A *very low* or *low* communication level was observed in 21% of patients and 11% of carriers.

TABLE 1 Social and demographic variables in patients and carriers for the TTR-FAP Val30Met

		TTR-FAP Val30Met (*n* = 115)		TTR-FAP Val30Met pre-symptomatic (*n* = 28)		TTR-FAP Val30Met patients (*n* = 87)	
		n	%	*n*	%	*n*	%
Sex	Female	67	58.3	19	67.9	48	55.2
	Male	48	41.7	9	32.1	39	44.8
Disease status	Pre-symptomatic	28	24.3				
	Patients	87	75.7				
Education	≤4 years	14	12.2	0	0.0	14	16.1
	5-9 years	50	43.5	12	42.9	38	43.7
	≥10 years	51	44.3	16	57.1	35	40.2
Professional status	Employed	74	64.4	26	92.9	48	55.2
	Unemployed	12	10.5	2	7.1	10	11.5
	On sick-leave	5	4.3			5	5.7
	Retired	24	20.8			24	27.6
Marital status	Single	24	20.9	11	39.9	13	14.9
	In a couple	82	71.3	16	57.1	66	75.9
	Divorced	9	7.8	1	3.6	8	9.2
Children	Yes	74	64.3	15	53.6	59	67.8
	No	41	35.7	13	46.4	28	32.2
Number of children	1	50	67.6	10	66.7	40	67.8
	2	18	24.3	4	26.7	14	23.7
	3	5	6.8	1	6.6	4	6.8
	4	1	1.3			1	1.7
Age (y)		36.6 (±8.6)		32.1 (±7.4)		38.1 (±8.6)	

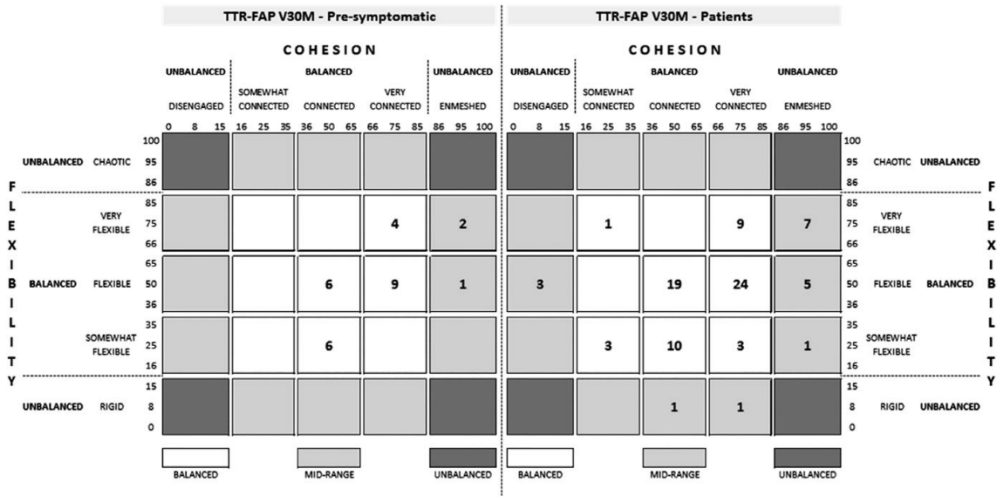

FIGURE 1 Graphical representation of TTR-FAP V30M pre-symptomatic carriers (n = 28) and patients (n = 87)

3.1.4 | Comparison of satisfaction levels

Satisfaction level was *high* or *very high* in 46% of the pre-symptomatic carriers and 47% of patients. *Very low* and *low* levels of satisfaction were manifested by 39% of carriers and 36% of patients. No significant differences were found between both groups.

TABLE 2 Social and demographic variables of carriers and their partners

		TTR-FAP Val30Met (n = 41)		Partners (n = 41)	
		n	%	*n*	%
Sex	Female	22	53.7	19	46.3
	Male	19	46.3	22	53.7
Sub-group	Pre-symptomatic	7	15.6		
	Patients	34	75.6		
Education	≤4 years	3	7.3	1	2.6
	5-9 years	20	48.8	21	53.8
	≥10 years	18	43.9	17	43,6
Professional status	Employed	32	78.0	35	89.7
	Unemployed	4	9.8	4	10.3
	On sick-leave	3	4.9		
	Retired	2	7.3		
Children	Yes	35	85.4		
	No	6	14.6		
Number of children	1	25	71.4		
	2	7	20.0		
	3	3	8.6		
Age (y)		37.44 (±6.76)		36.46 (±9.85)	

3.2 | TTR-FAP Val30Met patients and pre-symptomatic carriers vs their partners

This analysis included 82 participants (44 females and 39 males); TTR-FAP Val30Met pre-symptomatic carriers[7] and patients,[32] and respective partners were compared (Table 2).

3.2.1 | Scales scores of FACES IV dimensions

Most TTR-FAP Val30Met patients and carriers rated their families as *connected* (68%) or very *connected* (32%). On flexibility, 68% rated their family as *flexible*, 22% as *very flexible* and 10% as *somewhat flexible*. On the four unbalanced scales, most reported *very low* scores (88% disengaged, 68% enmeshed, 61% rigid and 85% chaotic).

Most partners (97%) rated their families as *very connected* or *connected*, and *flexible* or *very flexible* (93%). Most reported *low* or *very low* scores in the four unbalanced scales (Figure 2).

3.2.2 | Scales and ratios comparisons

TTR-FAP Val30Met patients and carriers had a median level of 65.0 for balanced cohesion and a median of 55.0 for balanced flexibility and the partners had a median score of 70.0 for balanced cohesion and a median of 58.0 for balanced flexibility. Unbalanced disengaged median was higher in carriers (16.0 vs 15.0), while unbalanced enmeshed, rigid and chaotic medians were the same. There were no significant differences.

Median cohesion and total ratios were lower in carriers vs partners (3.0 vs 3.5 and 2.6 vs 3.3), while median flexibility ratio was higher (2.5 vs 2.4); differences were not significant.

3.2.3 | Communication levels comparisons

Communication level was *high* or *very high* in 59% for TTR-FAP Val30Met patients and carriers and 71% for partners. A *very low* or *low*

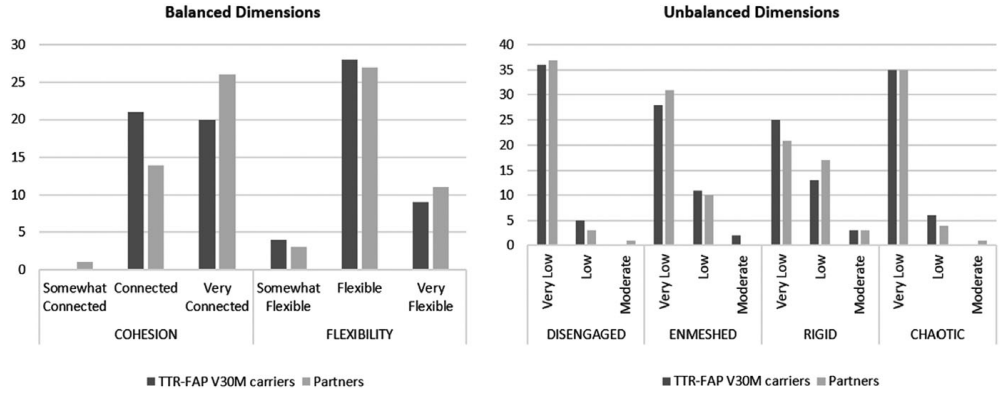

FIGURE 2 Scales scores in carriers and their partners

communication level was observed in 17% of TTR-FAP Val30Met carriers and in 12% of their partners.

3.2.4 | Satisfaction levels comparisons

Satisfaction level of TTR-FAP Val30Met carriers was *high* or *very high* for 39% and *very low* or *low* in 34%, while 38% of partners scored *high* or *very high* and 37% *very low* or *low*.

The differences found for communication and satisfaction were not statistically significant.

TABLE 3 Social and demographic variables of TTR-FAP Val30Met and MS patients

		TTR-FAP Val30Met (*n* = 34)		MS (*n* = 34)	
		n	%	*n*	%
Sex	Female	20	58.8	20	58.8
	Male	14	41.2	14	41.2
Education	≤4 years	1	2.9	3	8.8
	5-9 years	16	47.1	5	14.7
	≥10 years	17	50.0	26	76.5
Professional status	Employed	26	76.5	25	73.5
	Unemployed	4	11.8	4	11.8
	On sick-leave	1	2.9	1	2.9
	Retired	3	8.8	4	11.8
Marital status	Single	4	11.8	9	26.5
	On a couple	28	82.4	25	73.5
	Divorced	2	5.9		
Children	Yes	23	67.6	17	50.0
	No	11	32.4	17	50.0
Number of children	1	19	55.9	8	23.5
	2	3	8.8	8	23.5
	3	1	2.9	1	2.9
Age		35.15 (±6.42)		37.71 (±8.14)	

Abbreviation: MS, multiple sclerosis.

3.3 | TTR-FAP Val30Met vs MS patients

We finally studied a paired sample composed by 34 TTR-FAP Val30Met patients (48 females and 39 males) and 34 MS patients (20 females and 14 males). The two groups were paired regarding age, sex and functional status. MS patients had an EDSS <4.5 and patients with TTR-FAP Val30Met were in stage 1, which means they had minor motor disabilities. Sociodemographic variables are presented in Table 3.

3.3.1 | Scales scores and graphical representation of FACES IV

TTR-FAP Val30Met patients rated their family as *connected* (59%), *very connected* (35%) and 6% as *somewhat connected*; 94% rated their family as *flexible* or *somewhat flexible*; 6% as *very flexible*. On the four unbalanced scales, most patients reported *very low* to *moderate* scores. Disengaged was rated as *very low* by 94%, enmeshed was rated as *very low* or *low* by 91%, rigid was rated as *very low* or *low* by 88% and chaotic was rated as *very low* and *low* by 100%.

All patients with MS (100%) rated their families as *very connected* or *connected*. On flexibility, 56% rated their family as *flexible*, 41% *very flexible* and 3% *somewhat flexible*. On the four unbalanced scales, most patients reported *very low* or *low* scores (100% disengaged, 91% enmeshed, 79% rigid and 100% chaotic); 3% of MS patients perceived their family as having a *high* score for the rigid dimension.

Figure 3 shows the graphical representation of FACES IV results, regarding family functioning for TTR-FAP Val30Met and MS patients.

3.3.2 | Scales and ratios comparisons

Patients with TTR-FAP Val30Met had a median of 65.0 for balanced cohesion and a median of 55.0 for balanced flexibility. Patients with MS had a median of 82.0 for balanced cohesion and a median of 65.0 for balanced flexibility. These differences are statistically significant for both dimensions ($P < 0.001$ for balanced cohesion and $P < 0.01$ for balanced flexibility).

Unbalanced disengaged, enmeshed and chaotic median scores were higher in TTR-FAP compared to MS patients (15.0 vs 14.0; 20.0 vs 18.0; and 15.0 vs 14.0, respectively), but the dimension unbalanced

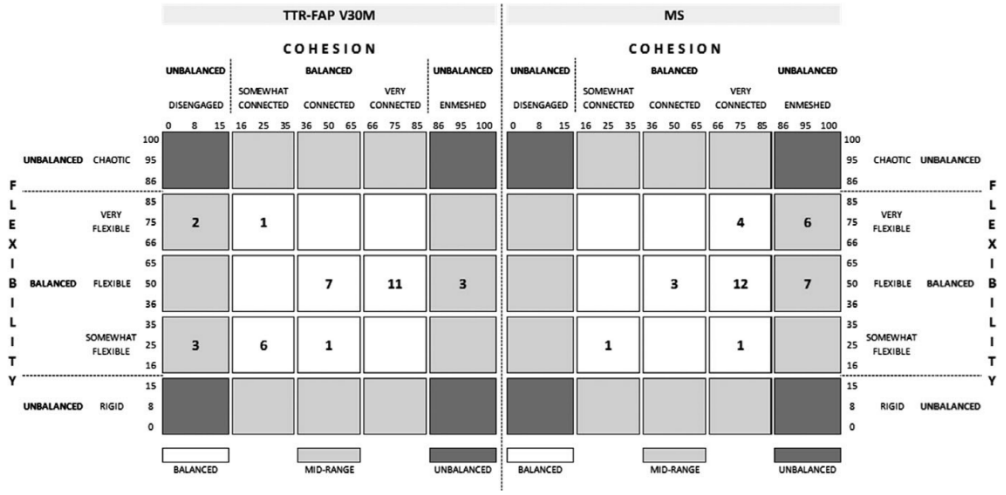

FIGURE 3 Graphical representation of TTR-FAP Val30Met (n = 87) and MS patients (n = 34)

TABLE 4 FACES IV ratios in TTR-FAP Val30Met and MS patients

	TTR-FAP Val30Met (n = 34)			MS (n = 34)			
	Median	Q1	Q3	Median	Q1	Q3	P
Cohesion ratio	3.10	2.32	4.29	4.84	3.84	5.47	<0.01
Flexibility ratio	2.33	1.71	3.43	2.90	2.13	4.19	NS
Total ratio	2.81	2.22	3.99	3.89	3.17	5.09	<0.01

Abbreviations: FACES IV, Family Adaptability and Cohesion Scale; MS, multiple sclerosis.

rigid was higher in the MS patients (25.0 vs 26.0); these differences were not statistically significant (median for both groups: 26.0).

Median values of cohesion and total ratios were statistically higher in MS patients (Table 4).

3.3.3 | Comparison of communication levels

Communication level was high or very high for 82% of MS patients, but only 53% for TTR-FAP patients. A *very low* or *low* communication level was observed in 9% of MS patients while is 18% in the TTR-FAP Val30Met patients. These differences are statistically significant (P < 0.01).

3.3.4 | Comparison of satisfaction levels

Satisfaction level was *high* or *very high* for 41% of TTR-FAP Val30Met patients and 67.7% of MS patients. *Very low* and *low* levels of satisfaction were manifested by 44% of TTR-FAP Val30Met patients. Differences were statistically significant (P < 0.05).

4 | DISCUSSION

Most participants perceived their families as balanced, both in terms of flexibility and cohesion scales. The descriptive statistics of FACES IV dimensions show that family functioning was perceived high in balanced and low in the extreme scales both for TTR-FAP Val30Met patients and pre-symptomatic carriers; data showed also a great similarity with their partners. Most families, according to Circumplex Model, could be considered as healthy (ratios above 1). Results pointed to a perceived less healthy family functioning in TTR-FAP Val30Met than MS patients.

According to the Family System Genetic Illness (FSGI) model,[33] TTR-FAP (similarly to HD) would imply intense anticipatory loss, as members of these families have high likelihood of developing a very severe disease, at a relatively predictable time of their life cycle.

Unlike HD, however, TTR-FAP Val30Met has some treatments, but these are not entirely effective or applicable to all patients. As in most inherited diseases, genetic testing is available, imposing psychosocial challenges on individuals and families, pre- and post-testing; knowledge about disease risks has an impact on family systems. Rolland emphasizes the pre-disease onset cycle, in addition to the chronic condition phase.[34] It is expected that disease phases and family cycles will interact continuously. A strong interference with the transitions in life cycle has been described in HD.[35]

Disruption caused by test results, altered expectations and possible future disturbing events, could also interfere with normal transitions in the family life cycle. Some families, although not all, will not manage to move forward.[4]

Results of this study are not consistent with Paneque´s, who used FACES III to evaluate subjects at risk for TTR-FAP, during genetic testing. In this study, families were perceived as highly flexible and

when unbalanced, tended to be chaotic[19] In addition to using a different version of FACES, they included both pre-symptomatic carriers and non-carriers, what may have contributed to the differences found.

TTR-FAP has a heavy psychosocial impact on individuals and families. Early parental disease and death are very common in these persons' lives. Many of these, during childhood and youth became carers of their parents. The disease and its life implications pose a significant psychosocial burden since childhood.[36] These patients and relatives are highly vulnerable to emotional stress and psychopathology during their lifetime. How will families cope with those burdens? On a dysfunctional way or through an adaptive organization that will protect the needs of their family members? In the present study, patients and pre-symptomatic carriers perceived their families as balanced and not dysfunctional, similar to their partners. We may consider family functioning as the result of a struggle between two "options" occurring on specific occasions in each family life and disease phase, but sometimes as a drift without options for every family. When a disease is recognized for several generations, an acquired "pattern" of transgenerational family structuring may occur and be determinant, less pathologic and more adaptive. In fact, an intergenerational flow of support and promotion of healthy behaviors across generations were described by Oliveira et al.[21] This intergenerational knowledge, along with a connected functioning in those families may act as a protective factor, contributing to more balanced results.

There are complex family processes, over time, when dealing with loss and death. Adaptive flexibility, continuity and cohesion/connectedness in the family system may require realignment of relationships and redistribution of roles to compensate for losses.[37] Stressful events in the family system and its members, will affect the whole unit, and may contribute either to a positive adaptation or to an individual or relational dysfunction.[38]

According to Walsh,[32,39] some risks for maladaptation exist (ambiguous loss, multigenerational legacy, no high levels of perceived communication), but we also need to consider other factors that could contribute to the presence of a high resilience in these families (coherence and shared challenge, knowledge about the disease, organizational family patterns) favoring adaptability. The high cohesion perceived by these subjects may respond to the higher needs of their families, facing all vicissitudes of a well-known disease occurring at several points of the family life cycle.

On the other hand, this higher cohesion does not seem to prevent the autonomy that allows them to pursue their lives, making new relationships and founding new families. In most patients and asymptomatic carriers, satisfaction levels were still high or very high, although lower than in MS patients. More significantly, balanced levels were found in MS, meaning that living with a hereditary disease, as TTR-FAP may be more stressful than with other chronic neurological diseases; additional factors (pre- and post-testing phases, decision-making processes about genetic testing and procreation, uncertainty about age-of-onset) must also be included in their experience.

Communication levels were perceived as low by some patients; but more partners saw it as low. Communication is crucial for transmission of useful information and open exchange of emotional contents among relatives. Communication styles are very important as the family is being put at the center of genetic risks information.[40,41] It is also essential to have in mind that sharing genetic information may also alter the relationships within the family.[3,41]

Although in the present study, the family as a unit was perceived mostly as healthy, complex psychological threats on every family member (patients, pre-symptomatic carriers, subjects still at risk, partners, carers, proven non-carriers or others) are continuously having an impact. These families need to be cared and their needs met, and communication difficulties need to be addressed.

4.1 | Conclusions

Family functioning was perceived as balanced by the vast majority of patients and pre-symptomatic carriers for TTR-FAP Val30Met, and these families were mostly healthy, according to Circumplex Model of Family Systems. Hereditary factor may be important to family functioning. Communication problems should be taken into account. Sharing information about genetic risks is not easy and may be a source of personal and familial conflicts. Thus, there is a need for genetic counseling and intrafamilial circulation of information on genetic risks. Our results point to possible protective or resilience factors; caring for these families as a unit is critical, while assisting individual members. This is disease with variable severity and age-at-onset, which may imply a diverse psychosocial impact in different families and individuals. It will be important to consider family support and family therapy in patients care assistance.

4.2 | Study limitations and further research

This sample included only Portuguese families with TTR-FAP Val30Met. Its results cannot be extended to different amyloidoses or to other populations. Although a smaller sample resulted from the paring with MS patients, the results of this comparison are important to be considered; however, a bigger sample will be necessary in order to evaluate if the genetic/familiar factor, influenced the familial dynamic. Other variables like sex, having affected offspring, among others, should be included in further research.

Further studies are needed to evaluate and compare family´s functioning in different phases of family life cycle and different phases of disease evolution. Differences between families that know the disease for several generations and those that face the disease for the first time, may be important and studies addressing these issues are also needed.

Conflict of interest

A.L. received honoraria from Pfizer for presentations at courses of TTR-related FAP. T.C. has received support from Pfizer, Ionis Pharmaceuticals and Alnylam Pharmaceuticals to attend scientific meetings. She integrates the speaker´s bureau of Pfizer, and received honoraria. J.S. has received in the past honoraria from Pfizer for presentations at genetic counselling of TTR-related FAP and courses, and for the preparation of leaflets and a webinar on genetic counseling.

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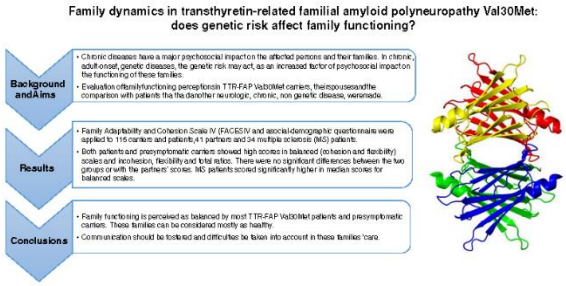
Graphical abstract

Family dynamics in transthyretin-related familial amyloid polyneuropathy Val30Met: Does genetic risk affect family functioning?

Alice Lopes, Carla Rodrigues, Isabel Fonseca, Alexandra Sousa, Margarida Branco, Teresa Coelho, Jorge Sequeiros, and Paula Freitas



CAPÍTULO 4

DISCUSSÃO E CONCLUSÕES FINAIS

1. Discussão

Pretendeu-se com este estudo avaliar consequências psicossociais da PAF-TTR Val30Met, o modo como afetavam as pessoas que dela sofrem ou podem vir a padecer, por um lado, e por outro, as implicações que a doença teria nas famílias.

Sendo uma doença hereditária, de início tardio, omnipresente no imaginário e na vida (real) das famílias afetadas, quisemos também perceber como estas duas vertentes se interligavam. As caraterísticas hereditárias e o início tardio na vida dos sujeitos impõem condições diferentes, por exemplo, de outras doenças crónicas em que tais circunstâncias não se verificam. Nestes pacientes com esta patologia hereditária, as representações da doença confundem-se com as narrativas da família, como se a família fosse a doença (Leite et al., 2016).

Esta discussão, que pretende ser geral e transversal, relembrará necessariamente as discussões incorporadas em cada artigo, reformulando-as e integrando-as numa perspetiva mais abrangente.

Constatou-se neste estudo que a maioria dos participantes, portadores da mutação Val30Met da TTR, teve sérias implicações relacionadas com a doença, em termos de acontecimentos de vida, desde idades muito precoces. A existência de um progenitor doente ou a sua perda, foram ocorrências frequentes antes da idade adulta. Alguns relataram que tiveram de mudar de casa ou vieram a ser cuidados apenas por um progenitor ou outro membro da família, e foram também relatadas perturbações psicológicas ou emocionais relacionadas com a doença. Desde muito cedo tiveram conhecimento da doença e das suas caraterísticas hereditárias. E, portanto, sabiam também, ainda que de forma mais ou menos vaga, do seu estado de risco genético.

A necessidade de cuidar do progenitor doente, papel que mais de metade dos participantes referiram ter assumido, foi também uma das conclusões do Questionário de História da Doença Pessoal e Familiar. Por um lado, ser ou ter sido objeto de cuidados parentais deficitários, por outro a mudança de papéis resultante da necessidade de prestar cuidados ao progenitor doente, parecem marcar a vida de uma parte significativa destas pessoas. Esta incapacidade de prestar cuidados parentais adequados foi realçada também em famílias com doença de Huntington (DH), doença neurológica com início também na idade adulta (Cerel, Fristad, Verducci, Weller, & Weller, 2006). Estes autores estudaram as consequências psicopatológicas da perda parental, e nomeadamente, a morte do progenitor durante a infância. Apesar da perda da mãe ser tida como mais traumática noutros trabalhos (Agid et al., 1999; Brown, Harris, & Copeland, 1977), naquele estudo isso

não foi encontrado. A situação de cuidadores dos pais, assunção de papéis adultos para os quais as crianças ou jovens não estão emocionalmente preparados, por vezes mesmo do papel parental (parentificação), tem sido referida em filhos de doentes crónicos em geral. Essas crianças corriam riscos de desenvolverem problemas psicológicos com maior *distress* emocional e comportamentos problemáticos, nomeadamente sexuais e de abuso de drogas (Lackey & Gates, 2001; Stein, Riedel, & Rotheram-Borus, 1999).

Quando inquiridos sobre antecedentes psiquiátricos ou psicológicos, a depressão e ansiedade foram os quadros predominantemente assinalados (em 26,5%), o que poderia representar alguma vulnerabilidade psicológica nesta população.

Perdas e lutos, ameaças permanentes duma doença presente na vida individual e familiar, e mudanças permanentes da normalidade de uma trajetória existencial, assim podem resumir-se as implicações que a doença pode ter.

As conclusões do primeiro estudo lançaram questões a que era necessário responder a seguir: se as pessoas afetadas pela mutação tinham mais problemas psicopatológicos do que a população em geral; e como se relacionavam estes com os acontecimentos de uma vida que parecia tão marcada pela doença e pelos acontecimentos com ela relacionados.

Os resultados do segundo estudo vieram confirmar que uma percentagem significativa de portadores sintomáticos e assintomáticos tinham índices mais elevados de psicopatologia que a população em geral, quando se consideravam os índices globais do BSI, e mais sintomas psicopatológicos assinalados. Na comparação dos dois grupos (sintomáticos e assintomáticos), o grupo daqueles que estavam já doentes apresentava mais problemas psicopatológicos, índices globais mais elevados e algumas dimensões do BSI (somatização, depressão, ansiedade e psicoticismo) eram também significativamente mais elevadas. Sendo a PAF uma doença crónica, estes resultados estavam de acordo quanto ao que já se sabia sobre as consequências psicopatológicas que as doenças crónicas médicas em geral tinham sobre os indivíduos que delas sofriam (W. Katon et al., 2007). Pensamos que é importante realçar que, tendo sido encontrado um número significativo de doentes com mais psicopatologia, deve, no entanto, considerar-se que tal como se verificou para outras doenças crónicas, a descompensação emocional é intermitente, isto é, além de momentos em que tal acontece serão de esperar outros em que a pessoa encontrará patamares de equilíbrio mediados por mecanismos de *coping* e adaptação. E devemos ainda considerar também que estes processos de adaptação às mudanças nunca estarão completos (Telford, Kralik, & Koch, 2006). O fato de a paramiloidose ser uma doença progressiva, em que vários fatores familiares podem atuar, imporá necessariamente patamares sucessivos de equilíbrio e desequilíbrio com que estas pessoas terão de lidar.

As mulheres, quer sintomáticas quer assintomáticas, eram mais vulneráveis para a sintomatologia psicopatológica. Nas mulheres doentes, todos os índices globais do BSI, bem com todas as dimensões do inventário, com exceção da somatização, eram mais elevados do que nos homens. Estes resultados estão de acordo com o que se sabe para a epidemiologia das doenças mentais em geral, em que o género feminino é mais vulnerável, nomeadamente para depressão e ansiedade (Kessler, 2003; Kuehner, 2016). Poderíamos pensar se as mulheres neste grupo particular, com esta doença, estariam mais sujeitas a viverem circunstâncias particulares que aumentasse a sua vulnerabilidade à psicopatologia, mas na realidade não encontramos nesta amostra uma maior sobrecarga nomeadamente relacionada com serem, por exemplo, mais vezes que os homens as cuidadoras dos progenitores doentes ou terem tido mais acontecimentos de vida relacionados com esta doença. A doença e os anos de doença foram também correlacionados positivamente com todos os índices globais do BSI e todas as suas dimensões. Este é um resultado que nos parece ser de realçar, já que a doença e as suas consequências têm na verdade um impacto psicopatológico muito importante e que é o mais determinante no estudo realizado.

Quando se analisaram os resultados apenas para os portadores assintomáticos, foi interessante verificar que as mulheres assintomáticas tiveram valores mais elevados do que os homens para a sensibilidade interpessoal e ansiedade fóbica, o que pode estar relacionado com mais dificuldades de relacionamento interpessoal neste grupo. É possível que o estado de risco genético ou de "doente à espera" e a angústia que lhe está associada, seja nas mulheres um fator de maior stress do que nos homens? E que este aumento de angústia possa estar ligado a um sentimento de desvalorização e menor autoestima, pela consciência da diferença e da presença de uma condição sobre a qual pode ser difícil falar?

É, no entanto, aqui já evidente que também os portadores assintomáticos da mutação demonstram, ainda sem as consequências mais imediatas da doença em si, uma vulnerabilidade aumentada aos sintomas psicopatológicos, distinta da população em geral. Este é um fato significativo que nos remete para a importância da vivência do risco por parte destas pessoas e também para as vicissitudes da sua existência, onde a presença da doença a nível familiar vai tendo as suas consequências na forma de acontecimentos objetivos (perdas e lutos) e subjetivos/psicológicos (expectativas e perdas antecipadas).

Este aspeto das doenças crónicas genéticas foi evidenciado por vários autores que propuseram modelos de compreensão distintos dos da doença crónica em geral (John S Rolland, 1987; J. S. Rolland, 2006; Street & Soldan, 1998). É identificada e descrita uma fase "pré-doença". Estes sujeitos em risco tendo vivido primeiro na incerteza do diagnóstico

e depois na angústia relacionada com o teste pré-sintomático, têm que se confrontar com uma espécie de luto antecipado em relação a um futuro que poderiam esperar (Sobel & Cowan, 2003). Depois, na sua condição já conhecida de portadores assintomáticos vivem na incerteza sobre o início da doença e muitas vezes, sobre a incerteza relacionada com escolhas reprodutivas. Segundo aqueles autores, era como se se pudesse instalar no sujeito uma "perda ambígua" (sem sentido e sem resolução) e um "luto sem direito", de um futuro "normal" que foi perdido.

Antes dos 14 anos, 25% dos portadores da mutação tinham já perdido o progenitor afetado e 44% tinham vivido com um progenitor afetado. Estes números parecem-nos bastante significativos. Embora não tenhamos estatísticas nacionais sobre a frequência da morte dos pais e de crianças que vivem com um progenitor com doença crónica, os estudos vivem com um progenitor com doença crónica, os estudos internacionais a que tivemos acesso, reportavam frequências manifestamente mais baixas que aquelas que encontrámos na população estudada (Berg, Rostila, & Hjern, 2016; Sieh, Visser-Meily, & Meijer, 2013).

A idade à morte do progenitor doente, durante a adolescência ou juventude, era um preditor de mais sintomas psiquiátricos na idade adulta. Ter menos de 14 anos aquando do início da doença no progenitor era também um preditor de maior gravidade de sintomas avaliada pelo Índice de Sintomas Positivos do BSI. As mudanças na vida familiar na infância relacionadas com a doença estavam também associadas a aumento de níveis de ansiedade.

A perda da mãe antes dos 14 anos afetou os sujeitos de modo mais significativo, em termos de índices psicopatológicos, nomeadamente somatização, sensibilidade interpessoal, ansiedade fóbica e ideação paranoide, os quais eram mais elevados que naqueles que tinham perdido o pai nessa idade. É interessante relacionar este fato com as respostas dada pelos participantes a propósito de quem os tinha cuidado após a morte do progenitor. Só uma percentagem muito pequena havia ficado com o pai após a perda da mãe, enquanto que no caso oposto, tinham permanecido quase sempre com a mãe ou com a mãe e outros membros da família. Tal pode significar que a disrupção familiar é maior quando era a mãe, com os filhos em idade precoce, que desparecia. A perda do pai afetava os sujeitos quando ocorria depois dos 25 anos o que relacionamos, como hipótese, com a perda de suporte na idade adulta mais ligada a questões sociais, financeiras ou de realização pessoal/profissional. Encontramos em alguns estudos sobre a morte do pai na infância, em geral, que esta era também um preditor para a existência de problemas mentais, duplicando o risco para a depressão major na idade adulta (Jacobs & Bovasso, 2009).

A influência da qualidade parental sobre o desenvolvimento social, emocional e comportamental é reconhecida, e as consequências da depressão dos progenitores no desenvolvimento psicossocial dos filhos têm sido apontadas (Barkmann et al., 2007; Thastum et al., 2009). No nosso estudo foram só consideradas as consequências, à idade adulta, das situações de perda parental. Parece, no entanto, fundamental que possam ser estudados os filhos destes indivíduos e avaliar de que modo a doença ou a presença da doença na família, pode influenciar o seu desenvolvimento psicossocial.

Outros fatores apareceram associados ao aumento de vulnerabilidade psicopatológica para várias dimensões do BSI, como ter filhos e estar profissionalmente inativo. Nesta doença, como em outras doenças crónicas, vários fatores de aumento de *stress* vão-se acumulando. Perder o emprego, com diminuição de capacidade financeira e perdas resultantes, poderão estar certamente relacionados e funcionar como fatores de *stress*. Alguns participantes referiram no Questionário Pessoal e Familiar da Doença, que tinham desistido da escola para ir trabalhar e ajudar ao suporte financeiro da família, corroborando esta questão. Ter filhos em situação de dificuldades físicas e sociais pode, sem dúvida constituir outro fator de *stress* resultando em aumento de vulnerabilidade psicopatológica. O desconhecimento do estatuto genético de risco nos filhos e a culpabilidade eventualmente ligada a esse fato, pode ser também geradora de *stress* psicológico.

Ser casado ou viver com alguém era preditor de níveis mais elevados de somatização. Apesar de *estar só* ser habitualmente um fator de agravamento das condições psicopatológicas ou estar associado a elas, por exemplo no caso da depressão, neste caso, não existiam diferenças entre as duas situações, exceto para aquela dimensão. Poder-se-ia pensar que nestes pacientes, em quem o corpo sofre muitas vezes enorme devastação, com interferências graves na área da sexualidade, e provavelmente com implicações na relação com o cônjuge, seria através do corpo, da somatização, que as perturbações emocionais se poderiam exprimir, e também através destes, corpo e sintomas, seria possível uma comunicação com o outro.

Nestes resultados obtidos, confirmou-se por um lado o que se esperava para uma doença crónica que tem enormes e muito importantes consequências devastadoras a níveis físico, funcional, social e relacional para o indivíduo. Nestes três primeiros estudos, parece ter sido confirmada também a interação constante entre a vida dos sujeitos, a doença e a família com permanentes intercorrências e penetrações mútuas. A doença crónica e, neste caso, a doença genética, incapacitante e progressiva, é muito mais do que a soma de sinais e sintomas físicos. Estes pacientes e pessoas em risco têm que enfrentar situações de crise que se sucedem (Dekkers, 2001), de diagnóstico, de patamares sucessivos de

adaptação a que têm de fazer face devido ao agravamento da doença e suas limitações, mas também em relação ao que vai acontecendo nos familiares próximos, também eles potenciais vítimas da doença.

Para além disto, pode existir uma necessidade de reestruturação permanente na vida do sujeito e na das suas famílias.

Têm sido cada vez mais valorizadas, na definição da família, as suas componentes emocionais e as trocas afetivas entre os seus membros. É na família, fonte principal na formação da identidade dos indivíduos, onde estes têm as suas primeiras experiências sociais e afetivas, essenciais para o desenvolvimento de estruturas biológicas, psicológicas e sociais (Erikson & Erikson, 1998).

As famílias em que a doença genética existe estão sujeitas a grandes sobrecargas psicológicas. Estas incidem primeiro sobre os seus membros individualmente. Perdas sucessivas, mas também vergonha social, estigma e por vezes isolamento social foram assinaladas nas famílias com doença de Huntington (Duisterhof, Trijsburg, Niermeijer, Roos, & Tibben, 2001; Van der Meer et al., 2006). Estes aspetos, bem como a existência de outras problemáticas psicossociais, poderiam levar a uma perda da qualidade de capacidades parentais, ficando as crianças expostas a consequências várias daí advindas, afetando entre outras a sua capacidade de vinculação, com influência no funcionamento adulto. Foi enfatizada nestes estudos, a importância em populações em que estas condições de maior vulnerabilidade, pudessem estar presentes. Esta importância relaciona-se por um lado com o papel chave que as relações de vinculação podem ter na transmissão transgeracional de dificuldades e privações e, por outro, pelo fato de pessoas com estilos de vinculação segura terem mais probabilidades de terem crianças com estilos de vinculação também seguros, o que por sua vez poderia ter implicações no funcionamento adulto e na psicopatologia.

Para além destes aspetos, já suficientemente importantes, encontramos outros na literatura que nos pareceram poder também justificar o conhecimento da vinculação nestes sujeitos. Os estilos de vinculação do adulto foram avaliados em sujeitos com doenças físicas e foi observado que estilos de vinculação inseguros se relacionavam com a existência de um maior número de sintomas médicos e com problemas na relação médico-doente e dificuldades na procura de cuidados (Barbosa et al., 2010; McWilliams & Bailey, 2010; McWilliams et al., 2000).

Os resultados do estudo 4 e do estudo preliminar apontam para a existência, nos portadores da “mutação”, de dimensões de vinculação medidas pela EVA, diferentes das

esperadas para a população geral. Embora estar doente tivesse sido o aspeto mais relevante associado com as dimensões inseguras, *ansiedade* (níveis mais elevados) e *conforto com a dependência* (abaixo dos normativos), também nos portadores assintomáticos se encontraram níveis diferentes dos esperados para a população geral.

Embora o estilo de vinculação seguro fosse o mais representado dos três, a maioria da amostra tinha estilos de vinculação inseguros, *ansioso* (em maior percentagem) bem como o *evitante.* Esta distribuição era diferente da encontrada para a população em geral num estudo de Shaver, em que o estilo de vinculação *seguro* era predominante e o *ansioso* o menos representado (Shaver & Mikulincer, 2002).

Foi encontrada no nosso estudo uma associação entre as dimensões inseguras da escala de vinculação do adulto e todos os índices globais psicopatológicos do BSI, bem como com a ansiedade e depressão. Estes resultados estão de acordo com o que seria esperado e de acordo com a literatura existente.

Tendo em conta os estudos anteriormente citados que relacionavam a vinculação com acontecimentos na infância, nomeadamente a indisponibilidade ou perda parental, procurámos ver se existiam alterações das dimensões de vinculação nos sujeitos que tinham assinalado tais perdas no seu percurso existencial. Os resultados encontrados para esta amostra, demonstraram que a morte ou doença do progenitor não eram preditores de níveis mais elevados das dimensões inseguras. Ao verificar se esta associação existia, admitíamos a continuidade dos processos de vinculação ao logo da vida e elementos de congruência entre a vinculação do adulto e a vinculação infantil (Fraley, Waller, & Brennan, 2000; Manassis, Owens, Adam, West, & Sheldon-Keller, 1999; Shevlin, Boyda, Elklit, & Murphy, 2014). No entanto, será necessário atender ao facto de a avaliação feita pelo instrumento usado se reportar, no fundamental, ao sistema de vinculação do adulto, com um suposto comportamental, atuado entre pares num âmbito de reciprocidade, ativado em situações de *stress* (Crowell & Treboux, 1995). Poderíamos admitir que a relação não encontrada entre estilos de vinculação e acontecimentos do passado poderia ter sido diferente se outro tipo de avaliação da VA, por exemplo a *"Entrevista de Vinculação do Adulto*", tivesse sido realizado. Perguntamo-nos, no entanto, também, se nestas famílias em que a doença é largamente reconhecida e existente nalgumas delas há várias gerações, poderão existir fatores adaptativos que permitiriam, apesar de tudo, uma substituição funcionante das figuras de vinculação na infância.

Os estilos de vinculação não são estáticos, mas dinâmicos ao longo da vida dos indivíduos e relacionados com situações de *stress* que os poderão determinar em situações de

ameaça. Tal circunstância poderia explicar o *estar doente* como a variável mais importante relacionada com os estilos inseguros de vinculação nesta população.

A presença nestes sujeitos, de modo significativo, de estilos e dimensões inseguras deverão ser relacionadas com dificuldades atuais e terão consequências nas suas vidas de adulto. Tais poderiam ser as que se relacionam com dificuldades nas suas relações interpessoais, nomeadamente afetivas e, porventura, nas que se relacionam com a disponibilidade para a procura de cuidados e nas necessidades que deverão ser compreendidas pelos profissionais de saúde que os atendem. A compreensão das caraterísticas psicológicas subjacentes aos estilos de vinculação é uma questão importante a ter em conta na abordagem psicoterapêutica e no apoio psicológico a estes sujeitos. Foi já assinalada a relação entre estilos de vinculação e estratégias associadas de *coping* associadas aos pedidos de ajuda (Bartholomew & Shaver, 1998). Num outro estudo mais recente, foi assinalada a importância dos estilos de vinculação enquanto possíveis fatores moderadores da transmissão intergeneracional de processos emocionais conflituais (Baptist, Thompson, Norton, Hardy, & Link, 2012).

Os resultados encontrados nos três estudos parcelares para avaliação do funcionamento das famílias em que existe a mutação Val30Met para a PAF-TTR indicaram que o funcionamento familiar nos portadores da mutação era percebido como equilibrado, tendo a maioria dos participantes níveis elevados nas escalas equilibradas do FACES IV, embora mais elevados na coesão e menores na flexibilidade. De acordo com este instrumento de avaliação, nenhuma família foi classificada como desequilibrada, nem se situava em nenhum dos extremos do gráfico que resulta da classificação obtida pela escala. Uma pequena percentagem das famílias situava-se na classificação *mid-range, o* que corresponde a situações em que, embora não havendo disfuncionalidade, poderão existir menores mecanismos intrafamiliares para lidar com mudanças necessárias e maior vulnerabilidade face a ameaças.

Os resultados obtidos eram semelhantes para portadores sintomáticos e assintomáticos assim como para os cônjuges ou companheiros. De acordo com o modelo circumplexo, estas famílias podiam considerar-se como tendencialmente saudáveis. A situação de doença não teve influência nos valores encontrados e poderia dizer-se que existe, ao longo do tempo e nas diferentes situações dos portadores (sintomáticos ou assintomáticos), estabilidade na perceção do funcionamento familiar.

Para testar a hipótese da influência hereditária na perceção do funcionamento familiar, foram feitas comparações com doentes que sofriam de esclerose múltipla, doença neurológica, também incapacitante e progressiva, mas não hereditária. Estes doentes

percecionavam o funcionamento familiar como mais equilibrado e tinham valores mais elevados nas escalas de comunicação e satisfação do que os portadores da "mutação" para a PAF-TTR. Estas diferenças, estatisticamente significativas, podem denotar uma tendência para um menor equilíbrio familiar, imposto pelo caráter hereditário da paramiloidose, quando comparadas com outras em que essa circunstância não existe.

No entanto, a inexistência de disfuncionalidade percecionada que encontramos, quando avaliada pelo modelo sistémico circumplexo de Olson, é certamente um fato muito relevante.

Sabe-se que a doença implica consequências psicossociais negativas importantes afetando os seus membros e a vida familiar, desde cedo nas suas vidas. E são também por eles apontadas, especificamente, implicações e mudanças na família que relatam como significativas.

Poderíamos assim esperar que alguns tivessem percecionado as suas famílias como disfuncionais, o que não aconteceu. Pensando na teoria de Rolland sobre as doenças crónicas, genéticas e hereditárias, a paramiloidose incluiria inúmeros elementos stressores, em vários momentos da existência dos sujeitos e das famílias.

Noutro estudo, em que a mesma metodologia empregue por nós também foi aplicada, foi encontrado algum grau de disfuncionalidade noutra doença hereditária de início tardio, a doença de Machado-Joseph (Bicudo Melo, 2013). Este facto poderia fazer pensar que alguns fatores protetores devem ser considerados nas famílias com a PAF-TTR que poderiam não estar presentes noutras patologias hereditárias.

Apesar de existirem riscos de desadaptação, lutos, "perdas ambíguas", legado multigeracional, comunicação intrafamiliar problemática, outros fatores poderiam contribuir para uma resiliência familiar. Estes poderiam ser o próprio conhecimento da doença, altamente reconhecida pelos seus membros nas famílias em que ela exista há mais de uma geração, a ameaça partilhada ou outros padrões organizacionais eventualmente favorecendo a adaptabilidade. Os níveis elevados de coesão percecionado por estes indivíduos, pode responder, em termos familiares, às necessidades aumentadas de proximidade entre os seus membros em resposta às vicissitudes impostas pela doença.

Walsh explica, a propósito da resiliência familiar, que a família pode ser uma resposta aos acontecimentos que ameaçam os indivíduos e que as famílias, nomeadamente em situações de crise, podem contribuir para uma adaptação positiva e um melhor funcionamento individual e relacional (Walsh, 2012, 2015).

É de admitir que estes fatores protetores possíveis, sejam também "hereditários", transmissíveis através da família, entre gerações, podendo pensar-se como modos transgeracionais de estruturação e organização familiar. Formas de proteção da família e dos indivíduos não seriam necessariamente conducentes a processos patológicos, mas antes mais adaptativos. Resultados coerentes com estes foram encontrados em famílias com esta doença, num fluxo de suporte e de promoção de comportamentos saudáveis transmitidos das gerações mais velhas para as seguintes (Oliveira, Mendes, & Sousa, 2017).

Os resultados dos estudos descritos nesta tese foram, por um lado, os esperados, mas por outro tiveram alguns aspetos menos esperados. Esperávamos, por exemplo, que as mulheres assumissem mais o papel de cuidadoras (o que era dito noutros estudos), que os acontecimentos infantis estivessem mais claramente relacionados com as alterações do estilo de vinculação, que as famílias fossem mais disfuncionais e que a comunicação fosse ainda mais problemática do que nos foi expresso.

Os resultados encontrados contêm, de uma determinada perspetiva, aspetos contraditórios e a necessitar de clarificação. Por um lado, foram encontrados acontecimentos relevantes desde a infância, com consequências também potencialmente relevantes em termos de psicopatologia associadas à doença ou à situação de portador assintomático. Alguns destes resultados de novo, foram associados positivamente a acontecimentos da infância destes sujeitos, nomeadamente perdas parentais e mudanças existenciais relacionadas com a doença durante a infância. Por outro lado, nos resultados relacionados com a vinculação do adulto, as alterações da VA foram associadas à doença, mas não aos acontecimentos infantis ou juvenis e finalmente nos estudos da família, estes tiveram resultados que definiram estas famílias como fundamentalmente funcionais.

Estamos então perante consequências psicológicas e psicopatológicas que se relacionaram com acontecimentos de vida, o que era que de certa forma esperado, e que se associaram a alterações da VA. No entanto, a VA não estava relacionada com as perdas infantis, e quer as suas alterações quer as consequências psicopatológicas encontradas, não se traduziram de forma negativa no funcionamento familiar que no geral se pode considerar saudável.

A família pode ser vista como promotora de estabilidade e contenção psicológica, mas também como fonte de conflitos e desequilíbrio. O conceito de resiliência familiar ultrapassa os limites dos seus membros individualmente, focando a unidade funcional familiar como fonte potencial de recursos para a resiliência individual face aos traumas individuais e sistémicos.

Este estudo, transversal e qualitativo, pode, no entanto, não captar necessariamente, as caraterísticas dinâmicas associadas à vivência familiar, e não distingue as fases de vida familiar. Estas fases podem, apesar de tudo, ser indiciadas através da comparação dos 2 grupos principais em estudo: sintomáticos e assintomáticos. Os assintomáticos, pessoas em média mais jovens, estarão em fases diferentes do ciclo de vida familiar em relação aos que estão já sintomáticos, mais velhos, o que pode permitir-nos concluir que, ainda assim, os resultados se mantêm.

Estudos conduzidos com outras metodologias, nomeadamente qualitativas, seriam importantes para esclarecer alguns destes aspetos levantados pelo presente estudo.

Estudos incidindo sobre cuidadores e membros saudáveis das famílias conduziriam a um reconhecimento importante sobre as consequências da doença nestes elementos e sobre as necessidades de suporte psicológico que eventualmente estes também precisem ter. As responsabilidades destes membros enquanto cuidadores, sobre quem recaem as necessidades elevadas de dependência dos membros doentes, são grandes, e certamente geradoras de sobrecarga psicológica.

Também não existem estudos sobre os elementos mais jovens, as crianças destas famílias, estudos que seriam certamente importantes para uma estruturação mais eficaz do apoio psicológico a estas famílias.

O funcionamento conjugal destes sujeitos necessitaria também de avaliação, já que a doença pode ter neste âmbito, múltiplas implicações.

Para além do apoio psicológico individual, a família terá de ser considerada como objeto de tratamento onde, para além da questão do seu funcionamento global como uma unidade, do funcionamento conjugal, terão de ser tomadas em consideração as que se relacionam com a comunicação intrafamiliar, quer do ponto de vista psicopedagógico, mas também em termos de comunicação emocional.

A abordagem das famílias e dos casais impõem a existência de terapeutas de família nas equipas terapêuticas, sobretudo nos centros mais especializados e de referência.

1.1. Limitações do Estudo

A configuração da amostra, composta só por participantes portugueses com PAF-TTR Val30Met, impede que estes resultados possam ser expandidos para outros doentes que, podendo ter a mesma mutação, pertençam a culturas e países diferentes, e, em alguns

casos, possam ter diferenças de apresentação clínica desta doença.

O tamanho pequeno de alguns grupos em estudo pode resultar em enviesamento dos resultados. Nomeadamente, inclui-se aí o grupo que denominamos como duvidosos e que seria interessante ser comparado com os outros, já que essa fase corresponde a grande incerteza que se admite ser geradora de angústia. O tamanho pequeno dos grupos quando se dividiam pelos que tinham vivido eventos infantis, pode ser também limitador. A obtenção de um tamanho maior de amostra, considerando estes grupos, será importante para futura investigação.

A avaliação psicopatológica através do *Brief Symptom Inventory* tem limitações quanto a fornecer diagnósticos psiquiátricos. Outras avaliações no âmbito da psicopatologia serão necessárias para corroborar os resultados agora encontrados, podendo aperfeiçoar os diagnósticos psiquiátricos nesta população.

Os eventos de vida avaliados disseram respeito aos que se relacionavam com a doença. Não foram inquiridos outros acontecimentos não relacionados, não tendo sido esse fato controlado nos resultados finais.

Finalmente, a utilização apenas de instrumentos quantitativos pode ser redutora na avaliação de questões psicológicas, numa doença em que a multiplicidade de fatores é complexa e em que os resultados do seu impacto psicossocial são também complexos, expressando-se em comportamentos, mas também em vivências psicológicas, por vezes difíceis de captar com os instrumentos usados.

2. Conclusões Finais

As conclusões a seguir enunciadas, resultam das respostas encontradas para cada um dos objetivos desta tese, tal como foram explicitadas a partir dos resultados dos estudos que a integram.

- O percurso existencial dos portadores de PAF-TTR Val30Met, sintomáticos e assintomáticos é marcado por acontecimentos de vida stressantes, relacionados com a doença, que se iniciam na infância, afetando o indivíduo e a família.

- A vivência da doença num dos progenitores ou da sua morte, e os impactos psicológicos durante a infância decorrendo dessas mudanças familiares são

relatadas pela maior parte dos sujeitos, e ocorreram até ao início da idade adulta. Isto implica que as crianças e adolescentes destas famílias necessitam de atenção por parte das equipas que apoiam psicologicamente estes portadores da mutação.

- A ocorrência mais tardia de acontecimentos stressantes relacionados com a doença foi também assinalada: a realização do teste pré-sintomático e a altura das decisões reprodutivas são momentos originadores de *stress* psicossocial.

- A presença de doença psiquiátrica ou problemas psicológicos sinalizados por médico ou psicólogo foi relatada em número significativo de participantes. A depressão e a ansiedade eram os diagnósticos referidos. É de esperar que a presença de fatores existenciais, potencialmente geradores de *stress* psicossocial, com o qual é preciso lidar, tornem estes sujeitos mais vulneráveis psicologicamente.

- Os doentes e os portadores assintomáticos apresentavam índices globais de psicopatologia mais elevados que a população geral. Isto significa que, numa percentagem bastante maior que a esperada, existe nestes sujeitos um maior número de sintomas psicopatológicos, com gravidade, apontando para situação de maior vulnerabilidade para *distress* psicológico ou distúrbio psiquiátrico.

- Estar já doente, os anos de doença e o sexo feminino eram os maiores preditores dos sintomas psicopatológicos associados.

- A doença, mas também a condição de risco genético, estavam associados a maior *distress* psicológico. Os portadores sintomáticos tinham valores mais elevados para algumas dimensões, nomeadamente depressão e ansiedade.

- A presença de eventos de vida stressantes, ligados à doença, na infância, adolescência ou juventude, estavam associados a maior vulnerabilidade para a existência de sintomas psicopatológicos na idade adulta.

- A morte ou doença do progenitor doente, vivida na infância ou juventude, estavam associados a níveis mais elevados dos índices psicopatológicos.

- A morte da mãe era um fator de *distress* na idade adulta, quando ocorria antes dos 14 anos. A morte do pai era preditora de mais psicopatologia no adulto, quando ocorria após os 25 anos.

- Os sujeitos que relatavam mudanças familiares, quer objetivas quer subjetivas impostas pela doença, no passado apresentavam maior *distress* psicológico.

- A vinculação do adulto diferia da distribuição da população normal. Muitos portadores sintomáticos, mas também assintomáticos, tiveram valores mais elevados na dimensão *ansiedade* e mais baixo na dimensão *conforto com a dependência.*

- Embora o estilo de vinculação segura fosse o mais representado, no seu conjunto os estilos inseguros de vinculação (ansioso e evitante) eram os mais representados, tanto em doentes como em portadores assintomáticos.

- As organizações de vinculação nesta população apontam para a existência de relações marcadas pelo medo de abandono e a dependência, pelo desconforto com a proximidade, evitantes, e com dificuldades na procura de ajuda.

- O funcionamento familiar avaliado pelo FACES IV e tendo como base o modelo sistémico circumplexo de famílias, era percecionado pelos participantes como fundamentalmente equilibrado e tendencialmente saudável.

- A avaliação dos cônjuges e companheiros era congruente com a percecionada pelos portadores da mutação.

- Quando comparados com doentes com esclerose múltipla, a nossa amostra apresentava *scores* mais baixos nas escalas equilibradas (coesão e flexibilidade) e não havia diferenças nas escalas desequilibradas (rígida, caótica, dispersa e emaranhada). Isto poderia significar que havia, tendencialmente, um pior funcionamento nestas do que nas famílias com esclerose múltipla, onde o fator hereditário não está presente.

- A comunicação era avaliada como baixa ou muito baixa em alguns sujeitos portadores da mutação. A satisfação e comunicação eram significativamente mais baixas nestes nossos participantes que nos doentes com esclerose múltipla.

- Algumas famílias, em percentagem não muito elevada, foram posicionadas como *mid-range* na representação gráfica do Modelo Circumplexo. Estas seriam famílias mais vulneráveis ao *stress* e ameaças ao funcionamento equilibrado.

- Tendo em conta as vulnerabilidades psicológicas individuais e familiares, impostas por uma doença que tem implicações reconhecidas pelos participantes, poderemos pensar se nesta doença particular e nestes sujeitos que na sua maioria provêm de famílias onde a doença é reconhecida há mais de uma geração pelo menos, existirão fatores protetores que permitam uma resiliência familiar que pode minimizar a ameaça de disfunção familiar.

- O risco individual de descompensação psicológica nesta população, o *stress* associado à vivência da doença, desde cedo, na vida destes sujeitos, e o seu impacto sobre as famílias, fazem com que o acompanhamento psiquiátrico e psicológico estruturado seja fundamental. Este é importante na altura da procura do teste pré-sintomático (como já previsto por lei no nosso país), mas também aquando das escolhas reprodutivas

- É, assim, fundamental que a avaliação e seguimento psicológico e o apoio psiquiátrico sejam incluídos nas equipas multidisciplinares que fazem o acompanhamento habitual de doentes e portadores assintomáticos.

- É necessário incluir a família como um todo e o casal nos cuidados a prestar, nomeadamente de âmbito psicológico. Isto significa que a presença de terapeutas familiares é também importante nessas equipas.

- É necessário olhar para outros membros da família, como objeto de cuidados e objeto de estudos posteriores. Neles se incluem os mais jovens, os cônjuges/companheiros, outros cuidadores e os elementos saudáveis da família.

- O enfoque nos problemas comunicacionais intrafamiliares, a passagem de informação do risco genético e comunicação emocional, são questões importantes que devem ser avaliadas para cada unidade familiar e ser objeto de apoio e facilitação, para que se obtenham melhores modos de lidar com as vicissitudes e ameaças ligadas à doença. A comunicação deve ser também uma questão a integrar na formação das equipas multidisciplinares.

- A participação regular de elementos da saúde mental na discussão dos pacientes permitirá melhorar a capacidade de diagnóstico psicopatológico dos restantes elementos permitindo uma maior sensibilização para os problemas psicológicos, os quais podem, por vezes, complicar as relações médico-paciente e piorar o acesso e prestação de cuidados de saúde. Esta participação permitirá também aos prestadores de cuidados de saúde mental, um maior conhecimento da doença, um melhor conhecimento dos doentes e das suas queixas, bem como uma partilha e aquisição de linguagem e cultura comum que beneficiará os doentes, mas também os prestadores de cuidados.

3. Perspetivas de Estudos Futuros

Deverão ser considerados no futuro, estudos que possam incluir as seguintes questões:

- Avaliação psiquiátrica com instrumentos mais discriminadores da psicopatologia.
- Avaliação psicopatológica comparativa entre grupos considerados mais vulneráveis: antes e depois do teste preditivo, antes do início da doença, primeiros sintomas, estádios diferentes da doença, fases de procriação**.**
- Inclusão na avaliação psicossocial de outros elementos das famílias, cuidadores e elementos saudáveis.
- Avaliação do ponto de vista de funcionamento psicológico, das crianças e adolescentes destas famílias.
- Avaliação qualitativa, nomeadamente da vinculação e do funcionamento das famílias.
- Avaliação do funcionamento do casal e da relação pais-filhos.
- Comparar o funcionamento familiar entre as famílias de novo e as famílias onde a doença é conhecida há mais gerações e confirmar se há ou não um elemento protetor e de resiliência maior nas famílias mais antigas.

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ANEXOS

Informação aos Participantes sobre o Estudo

centro hospitalar do Porto

DINÂMICAS FAMILIARES NA POLINEUROPATIA AMILOIDÓTICA FAMILIAR

Este é um estudo em desenvolvimento no Unidade Clinica de Paramiloidose do Centro Hospitalar do Porto e tem como objetivo o estudo da organização familiar e problemas emocionais decorrentes da doença. Assim esperamos melhorar a compreensão sobre os problemas psicológicos e relacionais das famílias onde a doença está presente podendo contribuir para a adequação e organização do apoio que necessitem.

A investigadora responsável por este estudo é a Dra Alice Lopes, médica psiquiatra, e diretora do serviço de Psiquiatria e Psicologia da Saúde, deste Hospital.

Farão parte deste estudo, as pessoas com diagnóstico de Polineuropatia Amiloidótica Familiar seguidos na Unidade Clínica de Paramiloidose deste Centro Hospitalar.

Pedimos assim, que preencha um questionário com o objetivo de recolher alguns dados pessoais; outro questionário em que terá de fornecer a opinião relativa à sua família; uma escala de avaliação da vinculação do adulto; e um inventário sobre sintomas psicopatológicos. O preenchimento destes questionários demorará cerca de 30 minutos.

Salientamos que toda a informação será confidencial e apenas os elementos da equipa de investigação a ela terão acesso. O armazenamento dos dados recolhidos será realizado de uma forma segura e o seu nome não estará presente.

Não é obrigado a participar; e caso decida não o fazer, não terá qualquer tipo de penalização.

Agradecemos desde já a sua participação e os Investigadores estão ao seu dispor para qualquer esclarecimento de dúvidas e para qualquer outra informação pertinente através do número: 222077500 – extensão: 1262.

Consentimento Informado 1
(Portadores Assintomáticos, Doentes com PAF e Doentes com EM)

CONSENTIMENTO INFORMADO

Dinâmicas Familiares na Polineuropatia Amiloidótica Familiar

Eu, abaixo-assinado _____ declaro ser maior de 18 anos e ter concordado, voluntariamente, em participar no projeto de investigação desenvolvido por Alice Lopes, médica psiquiatra, colaboradora da Unidade Clínica de Paramiloidose do Centro Hospitalar do Porto, Hospital Santo António, EPE.

Fui informado (a) de que o estudo de investigação acima mencionado se destina a analisar algumas variáveis presentes na organização familiar, e assim melhorar a compreensão sobre os problemas psicológicos e relacionais das famílias onde a doença está presente podendo contribuir para a adequação e organização do apoio que necessitem.

Sei que terei de preencher, inicialmente, um questionário com o objetivo de recolher alguns dados pessoais; outro questionário em que irei fornecer a minha opinião em relação à minha família; uma escala de avaliação da vinculação no adulto; e um inventário sobre sintomas psicopatológicos.

Sei que posso recusar-me a participar ou a interromper, a qualquer momento, a minha participação neste estudo, sem nenhum tipo de penalização por este facto.

Compreendi a informação que me foi fornecida, tendo oportunidade para realizar questões e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado, autorizando a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Data de participação: _____

Assinatura da Investigadora **Assinatura do(a) Participante**

_____ _____

Consentimento Informado 2
(Cônjuges)

CONSENTIMENTO INFORMADO

Dinâmicas Familiares na Polineuropatia Amiloidótica Familiar

Eu, abaixo-assinado _____ declaro ser maior de 18 anos e ter concordado, voluntariamente, em participar no projeto de investigação desenvolvido por Alice Lopes, médica psiquiatra, colaboradora da Unidade Clínica de Paramiloidose do Centro Hospitalar do Porto, Hospital Santo António, EPE.

Fui informado (a) de que o estudo de investigação acima mencionado se destina a analisar algumas variáveis presentes na organização familiar, e assim melhorar a compreensão sobre os problemas psicológicos e relacionais das famílias onde a doença está presente podendo contribuir para a adequação e organização do apoio que necessitem.

Sei que terei de preencher um questionário com o objetivo de recolher alguns dados pessoais e outro questionário em que irei fornecer a minha opinião em relação à minha família.

Sei que posso recusar-me a participar ou a interromper, a qualquer momento, a minha participação neste estudo, sem nenhum tipo de penalização por este facto.

Compreendi a informação que me foi fornecida, tendo oportunidade para realizar questões e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado, autorizando a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Data de participação: _____

Assinatura da Investigadora **Assinatura do(a) Participante**

_____ _____

ID: ☐☐☐

Questionário Sócio-Demográfico 1
(Portadores Assintomáticos, Doentes com PAF e Doentes com EM)

QUESTIONÁRIO

Data de avaliação:_____

A. CARACTERIZAÇÃO SOCIODEMOGRÁFICA

1. Data de nascimento: _____

2. Género:
- ☐ Feminino
- ☐ Masculino

3. Local de nascimento
3.1. Concelho:_____

4. Local de residência atual
4.1. Concelho:_____

5. Habilitações literárias (atendendo ao último ano completo):
- ☐ 1ºciclo (4ºano)
- ☐ 2ºciclo (6ºano)
- ☐ 3ºciclo (9ºano)
- ☐ Ensino secundário (12ºano)
- ☐ Ensino superior
- ☐ Nenhum

6. Profissão: _____
- ☐ Ativo
- ☐ Desempregado
- ☐ Baixa médica
- ☐ Reformado

6.1. Devido à doença?
- ☐ Sim
- ☐ Não

7. Estado civil:
- ☐ Solteiro
- ☐ União de facto
- ☐ Casado
- ☐ Viúvo
- ☐ Separado
- ☐ Divorciado

8. Tem filhos?
- ☐ Sim **8.1. Quantos:** _____
- ☐ Não

9. Com quem vive?
- ☐ Pais
- ☐ Filhos
- ☐ Cônjuge
- ☐ Sozinho
- ☐ Institucionalizado
- ☐ Outros **9.1. Especificar quem:** _____

ID: ☐☐☐ ☐☐

B. QUESTIONÁRIO DE SAÚDE MENTAL

1.Teve algum problema psicológico/psiquiátrico no último ano?

☐ Sim **1.1.** Indique qual?_____

☐ Não **(passe para a questão 2, por favor)**

1.2. Teve acompanhamento?

☐ Sim **1.2.1.** Indique quem o acompanhou. ☐ Médico de família

☐ Não ☐ Psiquiatra ou psicólogo

☐ Outro

2. Faz medicação psicofarmacológica?

☐ Sim **1.3.1.** Indique qual? _____

☐ Não

A PREENCHER PELA INVESTIGADORA

1. GRUPO:
☐ PAF
☐ ESCLEROSE

2. Subgrupo PAF:
☐ Assintomáticos
☐ Doentes

☐ Transplantados
☐ *Tafamidis*
☐ Estadio avançado
☐ Outros

3. Nº Processo: ☐☐☐☐☐☐☐

4. Ano de realização do Teste Preditivo: ☐☐☐☐

5. Já tem sintomas da doença?

☐ Sim **5.1.Indicar o ano:** ☐☐☐☐

☐ Não

6. Estadio de evolução da doença: ☐

7. Já realizou transplante hepático?

☐ Sim **7.1. Indicar o ano:** ☐☐☐☐

☐ Não

7.2.Está inscrito para transplante?

☐ Sim **7.2.1. Indicar o ano:** ☐☐☐☐

☐ Não

8. Está a tomar *Tafamidis*?

☐ Sim **8.1. Indicar o ano em que iniciou:** ☐☐☐☐

☐ Não

9. Tendo em conta as respostas da FACES IV, indicar:

9.1. Estrutura familiar:
☐ Família de origem
☐ Família nuclear
☐ Família monoparental
☐ Família alargada

9.2. Membro da família:
☐ Pai
☐ Mãe
☐ Filho

Questionário Sócio-Demográfico 2
(Cônjuges)

QUESTIONÁRIO

Data de avaliação:_____

A. CARACTERIZAÇÃO SOCIODEMOGRÁFICA

1. Data de nascimento: _____

2. Género:
- ☐ Feminino
- ☐ Masculino

3. Local de Nascimento
3.1. Concelho:_____

4. Local de Residência atual
4.1. Concelho: _____

5. Habilitações literárias (atendendo ao último ano completo):
- ☐ 1ºciclo (4ºano)
- ☐ 2ºciclo (6ºano)
- ☐ 3ºciclo (9ºano)
- ☐ Ensino secundário (12ºano)
- ☐ Ensino superior
- ☐ Nenhum

6. Profissão: _____
- ☐ Ativo
- ☐ Desempregado
- ☐ Baixa médica
- ☐ Reformado

7. Estado civil:
- ☐ Solteiro
- ☐ União de facto
- ☐ Casado
- ☐ Viúvo
- ☐ Separado
- ☐ Divorciado

ID: ☐☐☐ ☐☐

Questionário Doença e Família

DOENÇA E FAMÍLIA

1. **Teve contato com algum doente com PAF antes de saber que era portador?**
   - ☐ Não
   - ☐ Sim **1.1. Quem?**
     - ☐ Avós
     - ☐ Pais
     - ☐ Tios
     - ☐ Outro (familiar)
     - ☐ Outro (não familiar)
2. **Quem é o progenitor transmissor**
   - ☐ Mãe
   - ☐ Pai
   - ☐ Não tenho conhecimento
3. **Atualmente o progenitor transmissor é:**
   - ☐ Vivo **3.1. Tem sintomas da PAF?**
     - ☐ Sim
     - ☐ Não (passe para a questão 5)
   - ☐ Falecido **3.2. Que idade tinha quando o progenitor transmissor faleceu?**
     - ☐ Menos de 10 anos
     - ☐ 10 a 14 anos
     - ☐ 15 a 24 anos
     - ☐ Mais de 25 anos

   3.3. Que idade tinha quando o progenitor transmissor adoeceu?
   - ☐ Menos de 10 anos
   - ☐ 10 a 14 anos
   - ☐ 15 a 24 anos
   - ☐ Mais de 25 anos

   3.4. Cuidou do progenitor transmissor?
   - ☐ Não
   - ☐ Sim

4. **A doença na sua família de origem trouxe alterações ou mudanças para si?**
   - ☐ Não
   - ☐ Sim **4.1. Qual (ais)?**
     - ☐ Habitação
     - ☐ Local de residência
     - ☐ Agregado Familiar
     - ☐ Psicológicas. Quais? _____
     - ☐ Outras. Quais? _____

5. **Quem cuidou de si durante a sua infância:**
   - ☐ Pai
   - ☐ Mãe
   - ☐ Outro (familiar)
   - ☐ Outro (não familiar)
6. **Tomou conhecimento do resultado do Teste Preditivo:**
   - ☐ Logo após a sua realização
   - ☐ Anos após a sua realização
   - ☐ Após o aparecimento dos sintomas
   - ☐ Não sabe
7. **O diagnóstico da doença provocou alterações na sua família?**
   - ☐ Não
   - ☐ Sim **8.1. Descreva qual:** _____

ID: ☐☐☐ ☐☐

BSI

L. R. Derogatis; 1993; Versão: M. C. Canavarro; 1995

A seguir encontra-se uma lista de problemas ou sintomas que por vezes as pessoas apresentam. Assinale num dos espaços à direita de cada sintoma, aquele que melhor descreve o GRAU EM QUE CADA PROBLEMA O INCOMODOU DURANTE A ÚLTIMA SEMANA. Para cada problema ou sintoma marque apenas um espaço com uma cruz. Não deixe nenhuma pergunta por responder.

Em que medida foi incomodado pelos seguintes sintomas:	**Nunca**	**Poucas vezes**	**Algumas vezes**	**Muitas vezes**	**Muitíssimas vezes**
1. Nervosismo ou tensão interior	☐	☐	☐	☐	☐
2. Desmaios ou tonturas	☐	☐	☐	☐	☐
3. Ter a impressão que as outras pessoas podem controlar os seus pensamentos	☐	☐	☐	☐	☐
4. Ter a ideia de que os outros são culpados pela maioria dos seus problemas	☐	☐	☐	☐	☐
5. Dificuldade em se lembrar de coisas passadas ou recentes	☐	☐	☐	☐	☐
6. Aborrecer-se ou irritar-se facilmente	☐	☐	☐	☐	☐
7. Dores sobre o coração ou peito	☐	☐	☐	☐	☐
8. Medo na rua ou praças públicas	☐	☐	☐	☐	☐
9. Pensamentos em acabar com a vida	☐	☐	☐	☐	☐
10. Sentir que não pode confiar na maioria das pessoas	☐	☐	☐	☐	☐
11. Perder o apetite	☐	☐	☐	☐	☐
12. Ter um medo súbito sem ter razão para isso	☐	☐	☐	☐	☐
13. Ter impulsos que não se podem controlar	☐	☐	☐	☐	☐
14. Sentir-se sozinho mesmo quando está com mais pessoas	☐	☐	☐	☐	☐
15. Dificuldade em fazer qualquer trabalho	☐	☐	☐	☐	☐
16. Sentir-se sozinho	☐	☐	☐	☐	☐
17. Sentir-se triste	☐	☐	☐	☐	☐
18. Não ter interesse por nada	☐	☐	☐	☐	☐
19. Sentir-se atemorizado	☐	☐	☐	☐	☐
20. Sentir-se facilmente ofendido nos seus sentimentos	☐	☐	☐	☐	☐
21. Sentir que as pessoas não são amigas ou não gostam de si	☐	☐	☐	☐	☐
22. Sentir-se inferior aos outros	☐	☐	☐	☐	☐
23. Vontade de vomitar ou mal estar do estômago	☐	☐	☐	☐	☐

ID: ☐☐☐ ☐☐

Em que medida foi incomodado pelos seguintes sintomas:	Nunca	Poucas vezes	Algumas vezes	Muitas vezes	Muitíssimas vezes
24. Impressão de que os outros o costumam observar ou falar de si	☐	☐	☐	☐	☐
25. Dificuldade em adormecer	☐	☐	☐	☐	☐
26. Sentir necessidade de verificar várias vezes o que faz	☐	☐	☐	☐	☐
27. Dificuldade em tomar decisões	☐	☐	☐	☐	☐
28. Medo de viajar de autocarro, de comboio ou de metro	☐	☐	☐	☐	☐
29. Sensação de que lhe falta o ar	☐	☐	☐	☐	☐
30. Calafrios ou afrontamentos	☐	☐	☐	☐	☐
31. Ter de evitar certas coisas, lugares ou actividades por lhe causarem medo	☐	☐	☐	☐	☐
32. Sensação de vazio na cabeça	☐	☐	☐	☐	☐
33. Sensação de anestesia (encortiçamento ou formigueiro) no corpo	☐	☐	☐	☐	☐
34. Ter a ideia que deveria ser castigado pelos seus pecados	☐	☐	☐	☐	☐
35. Sentir-se sem esperança perante o futuro	☐	☐	☐	☐	☐
36. Ter dificuldade em se concentrar	☐	☐	☐	☐	☐
37. Falta de forças em partes do corpo	☐	☐	☐	☐	☐
38. Sentir-se em estado de tensão ou aflição	☐	☐	☐	☐	☐
39. Pensamentos sobre a morte ou que vai morrer	☐	☐	☐	☐	☐
40. Ter impulsos de bater, ofender ou ferir alguém	☐	☐	☐	☐	☐
41. Ter vontade de destruir ou partir coisas	☐	☐	☐	☐	☐
42. Sentir-se embaraçada junto de outras pessoas	☐	☐	☐	☐	☐
43. Sentir-se mal no meio das multidões como lojas, cinemas ou assembleias	☐	☐	☐	☐	☐
44. Grande dificuldade em sentir-se "próximo" de outra pessoa	☐	☐	☐	☐	☐
45. Ter ataques de terror ou pânico	☐	☐	☐	☐	☐
46. Entrar facilmente em discussão	☐	☐	☐	☐	☐
47. Sentir-se nervoso quando tem de ficar sozinho	☐	☐	☐	☐	☐
48. Sentir que as outras pessoas não dão o devido valor ao seu trabalho ou às suas capacidades	☐	☐	☐	☐	☐

ID: ☐☐☐ ☐☐

Em que medida foi incomodado pelos seguintes sintomas:	Nunca	Poucas vezes	Algumas vezes	Muitas vezes	Muitíssimas vezes
49. Sentir-me tão desassossegado que não consegue manter-se sentado e quieto	☐	☐	☐	☐	☐
50. Sentir que não tem valor	☐	☐	☐	☐	☐
51. Ter a impressão que, se deixasse, as outras pessoas se aproveitariam de si	☐	☐	☐	☐	☐
52. Ter sentimentos de culpa	☐	☐	☐	☐	☐
53. Ter a impressão que alguma coisa não regula bem na sua cabeça	☐	☐	☐	☐	☐

ID: ☐☐☐ ☐☐

EVA

Escala de Vinculação do Adulto

EVA - M.C. Canavarro, 1995; Versão Portuguesa da *Adult Attachment Scale-R*; Collins & Read, 1990

Por favor leia com atenção cada uma das afirmações que se seguem e assinale o grau em que cada uma descreve a forma como se sente em relação às relações afectivas que estabelece. Pense em todas as relações (passadas e presentes) e responda de acordo com o que geralmente sente. Se nunca esteve afectivamente envolvido com um parceiro, responda de acordo com o que pensa que sentiria nesse tipo de situação.

	Nada característico em mim	Pouco característico em mim	Característico em mim	Muito característico em mim	Extremamente característico em mim
1. Estabeleço, com facilidade, relações com as pessoas.	☐	☐	☐	☐	☐
2. Tenho dificuldade em sentir-me dependente dos outros.	☐	☐	☐	☐	☐
3. Costumo preocupar-me com a possibilidade dos meus parceiros não gostarem verdadeiramente de mim.	☐	☐	☐	☐	☐
4. As outras pessoas não se aproximam de mim tanto quanto eu gostaria.	☐	☐	☐	☐	☐
5. Sinto-me bem dependendo dos outros.	☐	☐	☐	☐	☐
6. Não me preocupo pelo facto das pessoas se aproximarem muito de mim.	☐	☐	☐	☐	☐
7. Acho que as pessoas nunca estão presentes quando são necessárias.	☐	☐	☐	☐	☐
8. Sinto-me de alguma forma desconfortável quando me aproximo das pessoas.	☐	☐	☐	☐	☐
9. Preocupo-me frequentemente com a possibilidade dos meus parceiros me deixarem.	☐	☐	☐	☐	☐
10. Quando mostro os meus sentimentos, tenho medo que os outros não sintam o mesmo por mim.	☐	☐	☐	☐	☐
11. Pergunto frequentemente a mim mesmo se os meus parceiros realmente se importam comigo.	☐	☐	☐	☐	☐
12. Sinto-me bem quando me relaciono de forma próxima com outras pessoas.	☐	☐	☐	☐	☐
13. Fico incomodado quando alguém se aproxima emocionalmente de mim.	☐	☐	☐	☐	☐
14. Quando precisar, sinto que posso contar com as pessoas.	☐	☐	☐	☐	☐
15. Quero aproximar-me das pessoas mas tenho medo de ser magoado(a).	☐	☐	☐	☐	☐
16. Acho difícil confiar completamente nos outros.	☐	☐	☐	☐	☐
17. Os meus parceiros desejam frequentemente que eu esteja mais próximo deles do que eu me sinto confortável em estar.	☐	☐	☐	☐	☐
18. Não tenho a certeza de poder contar com as pessoas quando precisar delas.	☐	☐	☐	☐	☐

FACES IV

FACES IV

Versão Original: Gorall, D., Tiesel, J., & Olson, D., 2004;
Versão Portuguesa: Rolim, L., Rodrigues, C., Coelho, T. & Lopes, A., 2005

Leia cuidadosamente cada afirmação e assinale a opção de resposta que está mais de acordo com a perceção que tem da sua família.
Não há respostas "certas" nem "erradas", nem respostas para causar boa impressão. Por favor, não deixe nenhuma questão em branco.

Em que medida as seguintes afirmações descrevem a sua família...

		Não	Pouco	Em Parte	Em Geral	Muito Bem
1.	Os membros da família envolvem-se na vida um dos outros.	O	O	O	O	O
2.	A nossa família procura maneiras novas de lidar com os problemas.	O	O	O	O	O
3.	Dá-mo-nos melhor com os de fora do que entre nós.	O	O	O	O	O
4.	O tempo que passamos juntos é demasiado.	O	O	O	O	O
5.	Quando se que quebram as regras familiares há consequências rígidas.	O	O	O	O	O
6.	Parece que nunca nos organizamos na nossa família.	O	O	O	O	O
7.	Os membros da nossa família sentem-se muito próximos uns dos outros.	O	O	O	O	O
8.	Os pais consultam os filhos antes de tomarem decisões importantes.	O	O	O	O	O
9.	Quando estão em casa, os membros da famíia parecem evitar o contacto uns com os outros.	O	O	O	O	O
10.	Os membros da família sentem-se obrigados a passar juntos a maior parte do tempo livre.	O	O	O	O	O
11.	Há graves consequências quando um membro da família faz algo errado.	O	O	O	O	O
12.	Precisamos de mais regras na nossa família.	O	O	O	O	O
13.	Nos momentos dificéis, os membros da família apoiam-se mutuamente.	O	O	O	O	O
14.	Os filhos têm uma palavra a dizer na sua disciplina.	O	O	O	O	O
15.	Os membros da família sentem-se mais próximos dos de fora do que dos outros membros da família.	O	O	O	O	O
16.	Os membros da família são demasiado dependentes uns dos outros.	O	O	O	O	O
17.	Os membros da família têm uma regra para quase tudo o que possa acontecer.	O	O	O	O	O
18.	Nunca se faz nada na nossa família.	O	O	O	O	O
19.	Os membros da família consultam-se mutuamente para tomar decisões pessoais.	O	O	O	O	O
20.	Na resolução de problemas são tidas em conta as sugestões dos filhos.	O	O	O	O	O
21.	Quando há um problema para ser resolvido, os membros da família estão por sua conta.	O	O	O	O	O
22.	Os membros da família têm pouca necessidade de fazer amigos fora da família.	O	O	O	O	O
23.	É difícil alterar as regras familiares.	O	O	O	O	O
24.	Está pouco claro quem é o responsável pelas tarefas e actividades na nossa família.	O	O	O	O	O
25.	Os membros da família gostam de passar juntos parte dos tempos livres.	O	O	O	O	O
26.	Alternámos entre nós as responsabilidades domésticas.	O	O	O	O	O
27.	Esta família não tem actividades comuns.	O	O	O	O	O
28.	Sentimo-nos demasiado ligados uns aos outros.	O	O	O	O	O
29.	Quando uma tarefa atribuída a um membro da família, é difícil alterar essa situação.	O	O	O	O	O
30.	Não há quem mande nesta família.	O	O	O	O	O
31.	Apesar dos membros da família terem interesses individuais, continuam a participar em actividades familiares.	O	O	O	O	O
32.	As regras são estabelecidas em conjunto pelos membros da família.	O	O	O	O	O
33.	Os membros da família raramente dependem uns dos outros.	O	O	O	O	O
34.	Não gostamos que os membros da família tenham actividades extra-familiares.	O	O	O	O	O

		Não	Pouco	Em Parte	Em Geral	Muito Bem
35.	É importante seguir as regras na nossa família.	O	O	O	O	O
36.	Ninguém na nossa família parece ser capaz de manter o rumo sobre quais são as suas obrigações.	O	O	O	O	O
37.	Nesta família há um bom equilíbrio entre a autonomia e a proximidade.	O	O	O	O	O
38.	Quando os problemas surgem, comprometemo-nos.	O	O	O	O	O
39.	Cada membro da família sabe muito pouco acerca dos amigos dos outros familiares.	O	O	O	O	O
40.	Os membros da família sentem-se culpados quando querem passar algum tempo longe dela.	O	O	O	O	O
41.	Os membros da família sentem que devem concordar com o que a família decide fazer.	O	O	O	O	O
42.	É difícil dizer ao certo quem manda nesta família.	O	O	O	O	O
43.	Os membros da família sentem-se satisfeitos com o modo de comunicar entre si.	O	O	O	O	O
44.	Os membros da família são excelentes ouvintes.	O	O	O	O	O
45.	Os membros da família expressam afecto uns aos outros.	O	O	O	O	O
46.	Os membros da família são capazes de pedir aos outros membros o que necessitam.	O	O	O	O	O
47.	Os membros da família conseguem discutir calmamente os seus problemas.	O	O	O	O	O
48.	Os membros da família debatem entre si as suas ideias e convicções.	O	O	O	O	O
49.	Quando os membros da família colocam questões uns aos outros, recebem respostas francas.	O	O	O	O	O
50.	Os membros da família tentam compreender os sentimentos uns dos outros.	O	O	O	O	O
51.	Quando se zangam, os membros da família raramente dizem coisas negativas uns dos outros.	O	O	O	O	O
52.	Os membros da família expressam uns aos outros o que verdadeiramente sentem.	O	O	O	O	O

Agora, responda de acordo com o grau de satisfação que a apresenta, relativamente à sua família.

		Muito Insatisfeito	Algo Insatisfeito	Geralmente Satisfeito	Muito Satisfeito	Extremamente Satisfeito
53.	O grau de proximidade entre os membros da família.	O	O	O	O	O
54.	A capacidade da família lidar com o stress.	O	O	O	O	O
55.	A capacidade da família para ser flexível.	O	O	O	O	O
56.	A capacidade da família para partilhar experiências positivas.	O	O	O	O	O
57.	A qualidade da comunicação existente entre os membros da família.	O	O	O	O	O
58.	A capacidade da família para resolver os conflitos.	O	O	O	O	O
59.	O tempo que passam juntos em família.	O	O	O	O	O
60.	O modo como os problemas são debatidos.	O	O	O	O	O
61.	A justeza das avaliações na família.	O	O	O	O	O
62.	A preocupação que os membros da família demonstram ter uns com os outros.	O	O	O	O	O